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THE FAMILY HISTORY
IN PATIENTS WITH CONGENITAL HEART DEFECTS
A Review of 717 Cases

By

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A Thesis Presented to the Faculty of the
Yale University School of Medicine in
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IN PATIENTS WITH CONGENITAL HEART DISEASE
A Thesis of 112 Pages

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INTRODUCTION

The etiology of congenital heart defects is unknown for almost all cases; maternal viral infections in the first trimester and certain teratogenic drugs have been shown to produce cardiac anomalies, but only in a few per cent of affected persons. Chromosomal aberrations, recessive genes and other genetic factors have been postulated as etiologic agents, but little investigation has been done in this country to determine their significance. The present study was undertaken to gain a better understanding of the importance of genetics in congenital heart malformations. The major undertaking was to determine the prevalence of cardiac anomalies in the parents, siblings and offspring of a randomly selected sample of heart defects patients. In addition, chromosome studies were performed on a selected group of patients to see if there were any detectable and consistent abnormalities.

A review of the literature concerning the possible causes of congenital heart malformations is presented prior to the experimental work. To put the role of genetic factors into perspective, possible environmental influences are reviewed first, along with a discussion of potential interaction between the environment and genetics. The presence of genetic factors in complex syndromes which include heart defects is shown. In addition there is a discussion of the present knowledge of chromosome aberrations in cardiac anomalies, and an analysis of previous studies of the family history in patients with heart malformations.

INTRODUCTION

The study of congenital heart disease is one of the most important in the field of internal medicine. It is a disease which is usually diagnosed in the first few years of life, and which may lead to a premature death. The study of this disease is therefore of great importance to the physician. The purpose of this book is to provide a comprehensive review of the current knowledge of congenital heart disease, and to discuss the latest advances in the treatment of this disease. The book is divided into two main parts. The first part is devoted to a review of the basic principles of congenital heart disease, and the second part is devoted to a discussion of the latest advances in the treatment of this disease. The book is written in a clear and concise style, and is suitable for use by both the general practitioner and the specialist. It is a valuable addition to the library of any physician who is interested in the study of congenital heart disease.

REVIEW OF THE LITERATURE

Environmental Factors

One of the most intensely studied causes of congenital malformations including cardiac defects is the role of maternal viral infections. Although several organisms have been studied in this regard, the only virus with an undisputed relationship to the causation of cardiac anomalies is rubella (Higgins, 1964). Infection by rubella is associated with a high, but apparently variable, incidence of congenital heart defects in live born infants. Campbell (1961) found a "minimal figure" of 7%, while in a review of the literature, Lamy, deGrouchy and Schweisguth (1957) found that the incidence varied between 25 and 80%. In a study of the 1964 rubella epidemic, Banatvala, Horstmann, Payne and Gluck (1965) found that 17 of 20 patients with the rubella syndrome had a cardiac malformation. It is estimated that maternal rubella infections account for about 1-3% of congenital heart defects patients (Campbell, 1961; Gibson and Lewis, 1952).

The most common lesions in patients born after maternal rubella are patent ductus arteriosus (Gibson and Lewis, 1952; Campbell, 1961), and pulmonic stenosis (Sever, Nelson and Gilkeson, 1965). Campbell (1961) also observed a relatively high number of patients with atrial or ventricular septal defects; he was particularly impressed by the high proportion (6%) of patients in his series with a ventricular septal defect associated with a patent ductus arteriosus.

Environmental Factors

One of the most intensely studied causes of congenital malformations including cardiac defects is the risk of maternal viral infections. Although several organisms have been studied in this regard, the only virus with a well-documented relationship to the causation of cardiac anomalies is rubella (Burgess, 1964). Infection by rubella is associated with a high, but apparently variable, incidence of congenital heart defects in live born infants. Campbell (1961) found a point prevalence of 7%, while in a review of the literature, Jones, Ferguson and Schwesinger (1957) found that the incidence varied between 25 and 80%. In a study of the 1964 rubella epidemic, Bannister, Horstmann, Payne and Gluck (1965) found that 17 of 20 patients with the rubella syndrome had a cardiac malformation. It is estimated that maternal rubella infections account for about 1-3% of congenital heart defect patients (Campbell, 1961; Gibson and Lewis, 1952).

The most common lesions in patients born after maternal rubella are patent ductus arteriosus (Gibson and Lewis, 1952; Campbell, 1961), and pulmonary stenosis (Gibson and Lewis, 1952; Gibson, 1965). Campbell (1961) also observed a relatively high number of patients with atrial or ventricular septal defects; he was particularly impressed by the high proportion (52%) of patients in his series with a ventricular septal defect associated with a patent ductus arteriosus.

Alzamora-Castro and associates (1960) in Peru demonstrated that patent ductus arteriosus occurs more frequently in persons born at high altitudes. They found that 20% of their 110 patients with a patent ductus were born at an altitude above 4,000 meters; only 3% of their general hospital population were born in a comparable location. There were no known cases of maternal rubella to account for the prevalence of the defect.

Experimental evidence for the production of congenital heart defects secondary to anoxia during pregnancy came from Ingalls (1952). He found a 1.9% incidence of ventricular septal defects in mouse fetuses exposed to anoxia during gestation as compared to 0.2% of controls.

Fetal irradiation has been shown to increase the incidence of congenital malformations as a whole, possibly including cardiac anomalies. In 1959 Gentry, Parkhurst and Bulin published a study of birth and death certificates in New York State in which they found an increased percent of persons with congenital cardiovascular defects born in areas of the state with higher natural radiation levels. Obviously, however, a review of only birth and death certificates does not give a very accurate picture of the diagnosis in many instances.

A more reliable study of the possible influence of irradiation of the fetus is that of the offspring of women pregnant at the time of the World War II bombing in Japan (Warkany, 1961). There were more infants that expected with microcephaly and mental retardation among the live born offspring, but the number of cases of cardiovascular anomalies was unremarkable.

Alammar-Gustro and associates (1960) in their study

stated that patent ductus arteriosus occurs more frequently in persons born at high altitudes. They found that 5% of their 110 patients with a patent ductus were born at an altitude above 1,000 meters; only 1% of their general hospital population were born in a comparable location. There were no known cases of maternal rubella to account for the prevalence of the defect.

Experimental evidence for the production of congenital heart defects secondary to anoxia during pregnancy came from Ingalls (1952). He found a 1.5% incidence of ventricular septal defects in mouse fetuses exposed to anoxia during gestation as compared to 0.2% of controls.

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A more reliable study of the possible influence of radiation on the fetus is that of the offspring of women exposed at the time of the World War II bombing in Japan (Gorham, 1961). There were more infants that appeared with abnormalities and mental retardation among the live born offspring, but the number of cases of cardiovascular anomalies was unimpaired.

Drugs received by the mother during specific times of gestation may cause malformations of the heart and other organs. A high incidence of congenital cardiac defects has been found in children born to mothers taking thalidomide during pregnancy (Taussig, 1962). Other drugs which have been implicated with less documentation include quinine, aminopterin, cortisone and antibiotics (Higgins, 1964).

Maternal vitamin deficiency has been postulated as an etiologic factor on the basis of animal experiments, but such a finding has never been well documented in man (Warkany, 1944; Sobin, 1955).

Some studies of patients with congenital heart defects have shown an increased incidence of disturbances during pregnancy such as abnormal bleeding (Anderson, 1954; Lamy, deGrouchy, and Schweisguth, 1957). In a recent review of patients seen in a pediatric cardiac clinic, including the patients used for the present study, Whittemore (1966) found that 4.9% of her 717 patients with all types of cardiac malformations had a history of maternal bleeding in the first trimester. This rate was significantly greater than the 2.7% found in 641 patients with innocent murmurs used as controls ($p=0.02$). When the patients were divided into diagnostic categories, it was observed that the incidence of maternal bleeding was not increased in patients with a left-to-right shunt (3% incidence). However, the rate in all other cardiac patients combined was 8.2%, which was highly significant in comparison to the patients with innocent murmurs ($p=0.001$).

There is evidence that the mother during pregnancy of

gestation may cause malformations of the fetus and other organs. A high incidence of congenital cardiac defects has been found in children born to mothers taking thiazide during pregnancy (Terasig, 1962). Other drugs which have been implicated with fetal malformation include quinine, aminopurine, cortisone and salicylates (Lewin, 1964).

Maternal vitamin deficiency has been suggested as an etiologic factor on the basis of animal experiments, but such a finding has never been well documented in man (Morgan, 1965; Sobel, 1955).

Some studies of patients with congenital heart disease have shown an increased incidence of disturbances during pregnancy such as abnormal bleeding (Lewin, 1964; Lewin, 1965; and Sobel, 1955). In a review of patients seen in a pediatric cardiac clinic, including the patients used for the present study, Whittemore (1966) found that 4.7% of her 171 patients with all types of cardiac malformations had a history of abnormal bleeding in the first trimester. This rate was significantly greater than the 2.7% found in 641 patients with indeterminate cause as reported (1966). When the patients were divided into diagnostic categories, it was observed that the incidence of abnormal bleeding was not increased in patients with a left-to-right shunt (3% incidence). However, the rate in all other cardiac patients combined was 6.2%, which was highly significant in comparison to the patients with indeterminate cause (2.7%).

The patients with cyanotic malformations had the highest incidence of maternal bleeding in the first trimester (10.2%; $p=0.003$).

An unequal distribution of births throughout the year has been observed in some groups of patients. The importance of this finding is unclear. In a report by Rutstein and Nickerson (1952) there were significantly more patients with patent ductus arteriosus born in the months between October and January. They correlated this finding with the annual increase of rubella cases occurring in their state (Massachusetts) during the winter and early spring, the months when these pregnancies were in their first trimester. Other studies of the seasonal distribution of births in patients with patent ductus arteriosus have shown a different period of increased birth rates, and in these reports it has been impossible to relate the findings with epidemics of rubella or other disease. Anderson (1954) noted an excess of patients born between October and March, while Polani and Campbell (1960) had a higher frequency of females than expected born between August and October. McKeown (1953) observed a rise in females born in May through August. However, the patient populations used for the studies varied widely in location, ranging from Birmingham, England to Minneapolis, Minnesota. It is conceivable that there is a common, but unrecognized, etiologic factor in these groups of patients which differs in its time of action between the various geographical areas.

Interaction of Environmental and Genetic Factors

The genetic constitution of man can be altered by environmental conditions, such as exposure to excessive amounts of radiation. Advanced maternal age has also been postulated as an important factor in the alteration of genetic material. The classic example of the latter statement is the tremendous increase in the number of mongols born to women over 40 years of age (Nelson, 1964). Non-disjunction during meiosis is blamed for the trisomy of the #21 chromosome, the sine qua non of mongolism. A few of the studies of patients with congenital heart defects have demonstrated an advanced mean maternal age (Polani and Campbell, 1955; Richards, Merritt, Samuels, and Langmann, 1955), but others have reported a normal distribution of maternal ages (Record and McKeown, 1953; Lamy, deGrouchy and Schweisguth, 1957; Polani and Campbell, 1960; Campbell and Polani, 1961a; Campbell, 1962). Therefore, it does not seem likely that maternal age is very important in the etiology of isolated cardiac anomalies.

Birth rank is closely related to maternal age, but the two variables can be separated (Polani and Campbell, 1955). Holding maternal age constant, Lamy, deGrouchy and Schweisguth (1957) found a statistically significant difference between the mean birth rank in patients with heart malformations and that of a control group; the mean for the affected patients was 2.23 and for the controls 2.03. However, birth rank was not found to be a significant variable in the studies of Polani and Campbell (1955, 1960) or of Anderson (1954).

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The same has been observed in mongolism. A few of the children of pa-

tients with congenital heart defects have demonstrated an

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Richards, Purtilo, Samuel, and Langman, (1957) have shown

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(1957) found a statistically significant difference between

the mean birth rank in patients with heart malformations and

that of a control group; the mean for the control group was

was 2.17 and for the controls 1.97. However, birth rank was

not found to be a significant variable in the studies of

Poland and Campbell (1957, 1958) or of Johnson (1957).

Penrose (1955) believes that the critical measurement in a study of parental age is the difference between the paternal and maternal ages. In a group of patients with coarctation of the aorta, Campbell and Polani (1961b) found a statistically increased difference between the mean paternal and maternal ages in their patients as compared to a control group. An increased difference was also found in a group of patients consisting mostly of tetralogies of Fallot (Polani and Campbell, 1960). This variable has not been evaluated in most reports of patients with congenital heart defects.

Other possibly significant parameters involving the interaction of environment and genetics include the report by Dogramaci and Green (1947) that a very high percent of the fathers of their patients were employed in occupations involving the use of lead. No one has confirmed this observation. Murphy (1936) noted a period of decreased fertility prior to the conception of malformed children. However, Polani and Campbell (1955) found no period of infertility prior to the birth of the patients in their series.

Cardiac Malformations as Part of Complex Syndromes

A number of syndromes of varying etiology have congenital heart defects as an occasional or frequent associated malformation. A review of these syndromes and their causes is important in assessing the role of such factors in cardiac anomalies in general.

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Genetic Abnormalities as Part of Congenital Syndromes

A number of syndromes of varying extent have been reported

heart defects as an occasional or frequently associated feature

of them. A review of these syndromes and their causes is

important in assessing the role of such factors in genetic

anomalies in general.

There are several disease complexes with known familial tendencies in which cardiac malformations are a part of the clinical picture. The Ellis van Creveld syndrome, which is inherited as an autosomal recessive trait and is characterized by ectodermal dysplasia, chondrodysplasia, and polydactyly is often associated with a single atrium (Giknis, 1963).

Thirty to sixty percent of persons with Marfan's syndrome have cardiac defects including atrial septal defects (Steinberg, Mangiardi, and Noble, 1957). Aortic and mitral insufficiency have also been found. Very frequently these people develop medial necrosis of their aorta, which can extend into the aortic valve to cause insufficiency; it is a matter of semantics whether or not such lesions are congenital. Marfan's syndrome is inherited as a dominant characteristic (Nelson, 1964).

The Ehlers-Danlos syndrome (hypermobility and hyperelasticity of the joints and fragility of the skin) is related to Marfan's syndrome in that both are inheritable disorders of the connective tissue. Occasionally both diseases are found within the same family suggesting a common genetic background (Goodman, Wooley, Frazier, and Covault, 1965). Atrial septal defects, tetralogy of Fallot, aneurysm of the sinus of Valsalva with aortic insufficiency, and mitral and tricuspid insufficiency are known to occur with this syndrome (Fantl, Momis and Sawers, 1961; Wallach and Burkhart, 1950; Tucker, Miller, and Jacoby, 1963; Madison, Bradley, and Castillo, 1963).

There are several clinical conditions which have been
mentioned in which certain malformations are a part of the
clinical picture. The Ellis-van Creveld syndrome, which is
inherited as an autosomal recessive trait and is character-
ized by acromesomelic dysplasia, chondrochondrodysplasia, and poly-
dactyly is often associated with a single disease (Ellis, 1961).
Thirty to sixty percent of persons with Marfan's syndrome
have cardiac defects including aortic aortic defects (Gorlin,
Berg, Hirschfeld, and Hodge, 1957). Aortic and mitral insuffi-
ciency have also been found. Very frequently these people
develop aortic aneurysms of their aorta, which can rupture and
be fatal. Some people also have aortic stenosis. It is a matter of
debate whether or not such lesions are congenital. Marfan's
syndrome is inherited as a dominant characteristic (Marfan,
1946).

The Marfan-Danlos syndrome (hypermobility and hyper-
elasticity of the joints and fragility of the skin) is related
to Marfan's syndrome in that both are inherited as autosomal
dominant traits. Occasionally both diseases are
found within the same family suggesting a common genetic basis
(Goodman, Weis, Fraser, and Gorman, 1962). The
clinical picture, pathology of Marfan's syndrome is the same as
Marfan's with aortic insufficiency, and aortic and mitral
insufficiency are known to occur with this syndrome (Marfan,
1946; Goodman and Gorman, 1962; Gorman and Goodman, 1962; Gorman,
Weis, and Gorman, 1962; Gorman, Weis, and Gorman, 1962).

Cardiac anomalies, especially atrial septal defects, are also found with inherited malformations of the upper extremities (Holt and Oram, 1960). This association is of particular interest, as is the presence of cardiac anomalies in babies with phocomelia born to mothers taking thalidomide, because of the simultaneous embryological development of the heart and the upper limbs (Arey, 1954).

McLoughlin, Krovetz, and Scheibler (1964) recently reviewed the literature of 330 cases of the Laurence-Moon-Biedl-Bardet syndrome. This hereditary disorder is transmitted by an autosomal recessive gene and is characterized by obesity, polydactylism, retinitis pigmentosa, mental retardation and hypogonadism. The authors found nine cases in the literature with cardiac involvement including a ventricular septal defect with pulmonic stenosis, patent ductus arteriosus, atrial septal defect, corrected transposition, and dextrocardia. They added two patients of their own who were brothers. One boy had the tetralogy of Fallot and the other, transposition of the great vessels.

The Kartagener's triad of bronchiectasis, chronic sinusitis and dextrocardia is another inherited disorder involving a heart anomaly (Nelson, 1964). Fanconi's anemia (congenital aplastic anemia) is occasionally accompanied by a malformation of the heart (McKusick, 1964).

Disorders related to chromosomal aberrations frequently have cardiac anomalies as a part of the clinical picture.

cardiac anomalies, especially septal defects, are also found with isolated malrotation of the upper extremities (Holt and Gray, 1961). This association is of particular interest, as is the presence of cardiac anomalies in babies with phocomelia born to mothers taking thalidomide, because of the simultaneous morphological development of the heart and the upper limb (Gray, 1954).

McLaughlin, Novata, and Schreiber (1964) recently reviewed the literature of 330 cases of the Langer-Siebert-Bardet syndrome. This hereditary disorder is characterized by an autosomal recessive gene and is characterized by obesity, polydactyly, ectopic sigmoid, ventral rotation and hypogonadism. The authors found nine cases in the literature with cardiac involvement including a ventricular septal defect with pulmonary stenosis, patent ductus arteriosus, atrial septal defect, corrected transposition, and others. They added two patients of their own who were brothers. One boy had the pathology of aortic and the other, transposition of the great vessels.

The Kartagener's triad of bronchiectasis, sinusitis and dextrocardia is another triad of disorder involving a heart anomaly (Wilson, 1964). Kartagener's anomaly (congenital dextrocardia) is occasionally accompanied by a malrotation of the heart (McDonald, 1964).

Distortions related to abnormal rotation frequently have cardiac anomalies as a part of the clinical picture.

Mongolism (trisomy 21), and the Trisomy 13-15 and 16-18 syndromes are the best examples of this association. In a study of 184 mongoloid children in which the cardiac status was proven by catheterization, angiography or autopsy in 98 cases, 70 had a congenital heart defect (Rowe and Uchida, 1961). Endocardial cushion defects accounted for 36% of the heart malformations; other anomalies were ventricular septal defects, 33%, patent ductus arteriosus, 10%, and ostium secundum, 9%. The prevalence of heart defects in other series of mongols is considerably lower. Berg (1960) estimated that 19% of mongols have cardiac anomalies. Undoubtedly the varying figure reflects differences in the age of the population being studied, since the death rate for mongols during the first year of life is directly related to the presence of heart malformations (Rowe and Uchida, 1961).

Persons with the Trisomy 13-15 syndrome usually, but not always, have a congenital heart defect along with their multiple anomalies (Rosenfield, Breibart, Isaacs, Klevit and Mellman, 1962; Pateau, Therman, Smith, Inhorn, and Wagner, 1960; Smith, Pateau, Therman, Inhorn, and DeMars, 1963). Most frequently the heart malformation is a ventricular septal defect, although anomalous pulmonary and systemic venous return, atrial septal defects, pulmonic stenosis, partial dextrocardia, endocardial fibroelastosis and other anomalies have been described.

The 17-18 trisomy is also associated with a high incidence of cardiac deformities (Hecht, Bryant, Motulsky, and Giblett, 1963; Smith, Pateau, Therman and Inhorn, 1960; Uchida,

Bowman, and Wang, 1962; Finley and Finley, 1963; Lewis, 1964). Again ventricular septal defects are the predominant lesion, although patent ductus arteriosus and atrial septal defect are also common.

Malformations of the heart are occasionally absent in both of these trisomy syndromes, even at autopsy (Atkins and Rosenthal, 1961; Townes, Kreutner, Kreutner, and Manning, 1963). Thus, it cannot be said that there is a direct causal relationship between an extra 13-15 or 16-18 chromosome and cardiac anomalies. However, the presence of the extra genetic material in some way increases the chance of developing heart malformations.

Patients with chromosomal abnormalities other than these three trisomy states have also been found to have cardiac deformities more frequently than expected. In one series of 25 girls with Turner's syndrome (XO sex chromosomes), 13 had a congenital heart defect (Lemli and Smith, 1963). Nine of the 13 girls had coarctation of the aorta. Pulmonic stenosis is also encountered with Turner's syndrome (Rainier-Pope, Cunningham, Nadas, Crigler, 1964). Patent ductus arteriosus was present in two of eight reported cases of persons with XXXXY sex chromosomes (Joseph, Anders and Taylor, 1964). There does not appear to be an increased incidence of heart malformations in patients with an XXY or XXX karyotype (McKusick, 1964).

sepal lobes are also common.

Relationships of the heart are considered in terms of both of these primary systems. Thus, at autopsy (Lacina and Rosenthal, 1961; Jones, Brumley, Freeman, and Loring, 1963). Thus, it cannot be said that there is a direct causal relationship between an extra 12-15 or 16-17 circumference and cardiac anomalies. However, the presence of the extra coronary material in some way increases the chance of developing such

Patients with chromosomal abnormalities other than Down's syndrome have also been found to have cardiac malformations more frequently than expected. In one series of 25 girls with Turner's syndrome (40 not chromosomal), 13 had a congenital heart defect (Lent and Smith, 1963). Nine of the 13 girls had coarctation of the aorta. Coarctation of the aorta is also encountered with Turner's syndrome (Kleinberg, 1963; Smith, 1963; Wright, 1963). Patent ductus arteriosus was present in two of eight reported cases of coarctation of the aorta (Lent and Smith, 1963; Smith and Taylor, 1963). There does not appear to be an increased incidence of heart malformations in patients with an XYY karyotype (McKusick, 1963).

Chromosome Studies in Persons with
Isolated Cardiac Defects

Chromosome analysis has been performed on patients with heart defects in the absence of other congenital anomalies by several groups. Book, Santesson, and Zetterquist (1961) studied a family in which a 49-year-old woman and her 14-year-old son had large secundum defects proven either by surgery or catheterization. An extra chromosome in the #19-20 group was found in both, and a #22 chromosome was missing in the boy. The father and sister were studied and found to have no evidence of heart disease or chromosomal abnormality.

A group in Japan (Sasaki, Makino, and Kajii, 1963) discovered a short #16 chromosome in nine of 22 patients with congenital heart defects. Six of the nine were thought to have atrial septal defects.

An elongation of a #16 chromosome was reported by Engel and associates (1966) in two siblings with ventricular septal defects. A third sibling in the family had the same cardiac lesion, but died before the chromosome studies were undertaken. The same chromosomal abnormality was identified in the maternal grandmother of these children, who had no evidence of a congenital heart malformation. Engel and co-workers (1966) also found a short arm in a member of the 13-15 pair in three siblings with atrial septal defects of the ostium secundum type. Relatives in this family with clinically normal hearts had normal karyotypes.

Chromosome analysis has been performed on patients with heart defects in the absence of other congenital anomalies by several groups. Bock, Gershwin, and Lederman (1967) studied a family in which a 49-year-old woman and her 11-year-old son had large secundum defects proven either by surgery or catheterization. An extra chromosome in the 15th group was found in both, and a 45,2 chromosome was missing in the boy. The father and sister were studied and found to have no evidence of heart disease or chromosomal abnormality. A group in Japan (Izumi, Nakano, and Taira, 1965) also covered a short 15 chromosome in nine of 25 patients with congenital heart defects. All of the cases were thought to have atrial septal defects. An elongation of a 15 chromosome was reported by Engel and associates (1966) in two siblings with ventricular septal defects. A third sibling in the family had the same cardiac lesion, but died before the chromosome studies were undertaken. The same chromosomal abnormality was identified in the maternal grandmother of these children, who had no evidence of a congenital heart malformation. Engel and co-workers (1966) also found a short arm in a number of the 15-17 pairs in three siblings with atrial septal defects of the secundum type. Relatives in this family with clinically normal hearts had normal karyotypes.

In spite of these positive findings, however, the evidence seems to favor the absence of specific chromosomal aberrations in patients with congenital heart defects. Anders, Moores and Emanuel (1965) recently reported chromosome studies on a series of 156 patients with cardiac deformities. The diagnosis was proven by surgery or catheterization in all but eight. In 22 of the patients, there was a history of a heart anomaly in a family member; all of these patients had normal karyotypes. Chromosomal variations were found in five persons, however, with a negative family history. These consisted of a shortening of a #16 in two persons with an ostium primum defect and an elongation of a #16 so that it resembled a #12 chromosome in two other patients. One of the latter patients had a patent ductus arteriosus, and the other, an atrioventricular canal with pulmonic valvular stenosis. An abnormal #15 was observed in a person with coarctation of the aorta. Chromosomal analyses were performed on the members of the immediate family of the patient with the patent ductus arteriosus. All three siblings had the same chromosomal variation, and in the two that were available for physical examination, no evidence of heart disease was found. Furthermore, all of the abnormalities observed by Anders and associates have been seen in normal persons of the general population. Thus, the authors feel that there is no evidence for a specific chromosomal variation in congenital cardiac anomalies. Other studies on smaller numbers of patients with heart defects support this impression (Warkany,

In order to obtain a more complete picture of the situation, a study was made of the records of the various hospitals and clinics in the city. It was found that the majority of the cases were of the chronic type, and that the patients were usually of the lower social class. The study also showed that the disease was more prevalent in the winter months, and that it was more common in the city than in the country. The results of the study are as follows:

1. The majority of the cases were of the chronic type.

2. The patients were usually of the lower social class.

3. The disease was more prevalent in the winter months.

4. It was more common in the city than in the country.

5. The results of the study are as follows:

a. The majority of the cases were of the chronic type.

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e. The results of the study are as follows:

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h. The disease was more prevalent in the winter months.

i. It was more common in the city than in the country.

j. The results of the study are as follows:

k. The majority of the cases were of the chronic type.

l. The patients were usually of the lower social class.

m. The disease was more prevalent in the winter months.

n. It was more common in the city than in the country.

o. The results of the study are as follows:

p. The majority of the cases were of the chronic type.

q. The patients were usually of the lower social class.

r. The disease was more prevalent in the winter months.

s. It was more common in the city than in the country.

t. The results of the study are as follows:

u. The majority of the cases were of the chronic type.

v. The patients were usually of the lower social class.

w. The disease was more prevalent in the winter months.

x. It was more common in the city than in the country.

y. The results of the study are as follows:

z. The majority of the cases were of the chronic type.

Weinstein, Soukup, Rubinstein and Curless, 1964; Book, Santesson and Zetterquist, 1961). However, the failure to identify chromosomal abnormalities with the present methods does not rule out their presence. Only very gross changes can now be detected; sub-microscopic changes are missed altogether, and these undoubtedly can cause multiple malformations. Furthermore, extensive surveys of chromosomal variations in a normal population are not yet complete, so that it is impossible to evaluate the finding of occasional minor changes in the karyotype. Thus, the answer to the question concerning the relationship between chromosomal changes and cardiac anomalies is still several years away.

Genetic Factors

Interest in the role of genetics in heart defects stems from observations of families in which there are several affected persons. The association of cardiac anomalies with the previously mentioned inherited disorders strengthens this argument. However, there are several serious problems with the hypothesis that heart malformations are genetically determined, as will be seen later. The remainder of this paper is an exploration of the evidence for and against genetic factors in this disease. It is recognized that genetics cannot account for all persons with heart defects. Nevertheless, it is important to ascertain whether any of these patients have inherited their lesion.

In a recent review of the evidence for genetic factors in all types of cardiovascular disease, McKusick (1964) listed six

Weinstein, Gossard, Kohnstien and Gossard, 1964; Gossard, Gossard and Gossard, 1964. However, the latter do identify chromosomal abnormalities with the present notions does not rule out their presence. Very few cases can now be detected; sub-microscopic changes are missed altogether, and these undoubtedly can cause multiple malformations. Furthermore, extensive surveys of chromosomal variations in a normal population are not yet complete, so that it is impossible to evaluate the finding of occasional minor changes in the karyotype. Thus, the answer to the question concerning the relationship between chromosomal changes and cardiac anomalies is still several years away.

Genetic Factors

Interest in the role of genetics in heart defects stems from observations of families in which there are several affected persons. The association of cardiac anomalies with the previously mentioned inherited disorders (Marfan's syndrome, etc.) is well known. However, there are several serious problems with the hypothesis that heart malformations are genetically determined, as will be seen later. The remainder of this paper is an exploration of the evidence for and against genetic factors in this disease. It is recognized that genetic factors are present for all persons with heart defects. Nevertheless, it is important to determine whether any of these persons have inherited their lesion.

In a recent review of the evidence for genetic factors in all types of cardiovascular disease, Gossard (1964) found that

approaches in determining whether genetics played a role in any specific disorder. They are: "familial aggregation, twin studies, interracial comparisons, genetics of pathogenetic components, blood-group-and-disease association, and animal homologies."

Familial aggregation and twin studies will be discussed at length later in this paper. No meaningful comparison of the incidence of congenital heart defects in different racial groups has been done; incidence figures have been quoted for several national groups, but the methods employed for the various studies have differed so much that interpretation of the results is impossible. McKusick (1964a) points out that there are a multitude of environmental variations between racial groups, in addition to differences of genetic constitution, making controlled studies difficult.

Sartor and Fraser (1964) compared the distribution of ABO blood groups in patients with cardiac malformations with a large series of healthy donors. In 268 persons undergoing surgery for a heart defect, he could find no statistical variation from his control group of 2,171 persons. Thus, there does not appear to be a genetic linkage between the gene loci for ABO blood groups and the loci, if one exists, for congenital heart defects.

The evidence for inheritance of heart malformations in animals was recently reviewed by Detweiler (1964). He noted an increase of specific cardiovascular anomalies in some strains. For example, ventricular septal defects are common in a particular line of inbred laboratory rats; subaortic stenosis is

found often in certain breeds of swine and ventricular septal defects in Hereford cattle. Congenital heart defects in general are encountered more frequently in pure bred dogs than in mongrels.

With this background, it will now be fruitful to investigate the familial aggregation of heart anomalies. The oldest known report of several afflicted persons within a family is that of two brothers who were found at autopsy in 1818 to have identical heart lesions; both had coarctation of the aorta, patent ductus arteriosus, ventricular septal defect and an over-riding pulmonary artery (cited by Snelling, 1937). Most of their ten siblings were said to have clinical evidence of cardiac defects.

A review of the literature concerning the presence of congenital heart defects in more than one member of a family was carried out. Many of the reports found during this search were insufficiently documented to be helpful in determining the genetics of specific cardiac lesions, or of heart malformations in general; cases in which the diagnosis for one or more member of the family was simply "congenital heart disease" or in which the relationship of the involved persons was not clearly stated, were omitted. Table 1 reviews families in which heart malformations appeared in more than one generation. Examples of more than one affected sibling are presented on Table 2. Instances of cardiac defects in twins will be considered separately.

found often in certain breeds of dogs and sometimes in cats. Defects in ventricular septum are also found in certain breeds of dogs and sometimes in cats. Defects in ventricular septum are also found in certain breeds of dogs and sometimes in cats. Defects in ventricular septum are also found in certain breeds of dogs and sometimes in cats.

With this background, it will now be possible to present the data on the familial aggregation of heart anomalies. The oldest known report of several affected persons within a family is that of two brothers who were found to be affected in 1810. Both had identical heart lesions; both had congenital aortic disease and patent ductus arteriosus, ventricular septal defect and an over-riding pulmonary artery (quoted by Snell, 1937). Most of their ten siblings were said to have clinical evidence of cardiac defects.

A review of the literature concerning the genetics of congenital heart defects is more than one hundred years old. Many of the reports found during this review were insufficiently documented to be included in this review. The genetics of specific cardiac lesions, or of heart malformations in general, comes in which the diagnosis for and the more number of the family was usually determined. In some cases or in which the relationship of the affected persons was not clearly shown, were omitted. Table 1 reviews families in which heart malformations appeared in more than one generation. Examples of more than one affected sibling are presented in Table 2. Examples of cardiac defects in twins are presented in Table 3. Examples of cardiac defects in twins are presented in Table 3. Examples of cardiac defects in twins are presented in Table 3.

Table 1
CONGENITAL HEART DEFECTS IN PARENTS AND THEIR CHILDREN
REVIEW OF THE LITERATURE

<u>AUTHOR</u>	<u>YEAR</u>	<u>RELATIONSHIP AND DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Debre et al	1923	mother - ventricular septal defect child - ventricular septal defect	clinical clinical
Walker	1934	father - coarctation of the aorta son - coarctation of the aorta	clinical clinical
Walker & Ellis	1940	father - patent ductus arteriosus 4 children - patent ductus arteriosus	unknown unknown
Barnes	1944	mother - atrial septal defect child - atrial septal defect	clinical clinical
Stein & Barber	1945	mother - coarctation of the aorta 2 children - male and female - patent ductus	clinical in all
Taussig	1947	grandfather - patent ductus arteriosus 2 of his children - patent ductus 1 of his grandchildren - patent ductus	not specified for any
Tucker & Kinney	1945	mother - ventricular septal defect 6 month fetus - ventricular septal defect	autopsy autopsy
Lamy & Schweisguth	1948	mother - patent ductus arteriosus daughter - patent ductus arteriosus	clinical clinical
Vakil & Daruwalla	1949	2 sisters - ventricular septal defect son of 1 sister - ventricular septal defect son and daughter of other sister - ventricular septal defect	clinical in all

REPORT OF DISCOVERY

LIST
OF THE DISCOVERIES
CONCERNING THE DISCOVERIES
AND THEIR DISCOVERIES

DISCOVERIES AND DISCOVERIES

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REPORT OF THE DISCOVERIES

Table 1 - continued

<u>AUTHOR</u>	<u>YEAR</u>	<u>RELATIONSHIP AND DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Campbell	1949	mother - patent ductus arteriosus daughter - coarctation of the aorta grandmother - atrial septal defect mother - atrial septal defect daughter - atrial septal defect	clinical clinical autopsy clinical clinical
Lamy & Schweisguth	1950	parent - ventricular septal defect and patent ductus arteriosus daughter - patent ductus arteriosus	clinical clinical
Cahen et al	1952	father - atrial septal defect son - atrial septal defect	autopsy catheterization
Starer	1953	mother - patent ductus arteriosus child - patent ductus arteriosus	not specified surgery
Taylor & Pollack	1953	mother - coarctation of the aorta son - coarctation of the aorta daughter - coarctation of the aorta	clinical autopsy angiography
Lewis et al	1958	mother - pulmonary valvular stenosis son - pulmonary valvular stenosis daughter - pulmonary valvular stenosis daughter - pulmonary valvular stenosis	catheterization catheterization catheterization clinical
Weinstein	1958	mother - atrial septal defect son - atrial septal defect	autopsy surgery
Davidson	1958	mother - atrial septal defect daughter - atrial septal defect son - atrial septal defect son - atrial septal defect	catheterization surgery catheterization clinical
Carleton et al	1958	2 sisters - atrial septal defect daughter of #2 - atrial septal defect and pulmonic stenosis	1. clinical 2. catheterization clinical

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Volume
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THE UNIVERSITY OF CHICAGO

COLLIER
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Судья

W. J. R. R. R.

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См. также статью "Вопросы - ответы"

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1. The first step is to identify the problem or question that needs to be addressed. This involves understanding the context and the specific requirements of the task.

ПОИСК

ДЛЯ КОПИРОВАНИЯ

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Table 1 - continued

<u>AUTHOR</u>	<u>YEAR</u>	<u>RELATIONSHIP AND DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Sissman et al	1959	grandmother - supravulvular aortic stenosis grandson - supravulvular aortic stenosis	autopsy autopsy
Campbell	1959	father - tetralogy of Fallot son - patent ductus arteriosus	surgery surgery
		mother - atrial septal defect child - tetralogy of Fallot	clinical autopsy
		mother - patent ductus arteriosus daughter - coarctation of the aorta	clinical clinical
		mother - pulmonary valvular stenosis daughter - patent ductus arteriosus	clinical surgery
		mother - aortic stenosis son - aortic stenosis	clinical clinical
		mother - atrial septal defect son - atrial septal defect	clinical surgery
		mother - ventricular septal defect son - ventricular septal defect	clinical clinical
Polani & Campbell	1960	mother - pulmonic stenosis child - patent ductus arteriosus	clinical not specified
Zetterquist	1960	3 sisters & 1 brother - atrial septal defect	1. clinical (? Dx. - died before study - no post mortem) 2. clinical 3. catheterization 4. surgery

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<u>AUTHOR</u>	<u>YEAR</u>	<u>RELATIONSHIP AND DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Zetterquist (cont.)	1960	son of #1 - atrial septal defect son of #2 - atrial septal defect son of #4 - atrial septal defect daughter of a normal sibling - atrial septal defect	surgery clinical catheterization clinical
Brent et al	1960	3 brothers - muscular subaortic stenosis son of #1 - muscular subaortic stenosis 3 brothers - muscular subaortic stenosis (nephews of #'s. 1, 2, & 3) son of #5 - muscular subaortic stenosis	1. autopsy 2. clinical 3. tenuous retrospect. 4. clinical 5. clinical 6. autopsy - clinical 7. tenuous - clinical 8. clinical
		4 siblings - muscular subaortic stenosis (3 female) half-sibling of 1,2,3,4 - muscular subaortic stenosis daughter of #1 - muscular subaortic stenosis daughter of #4 - muscular subaortic stenosis	1. autopsy 2. retrospective 3. clinical 4. clinical 5. retrospective 6. clinical 7. clinical
Burman	1961	1 brother & 2 sisters - patent ductus daughter of the male - patent ductus	surgery in all clinical
Campbell & Polani	1961a	father - atrial septal defect daughter - atrial septal defect mother - atrial septal defect son - atrial septal defect mother - atrial septal defect son - atrial septal defect	clinical surgery catheterization surgery clinical surgery

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Table 1 - continued

<u>AUTHOR</u>	<u>YEAR</u>	<u>RELATIONSHIP AND DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Campbell & Polani	1961b	mother - patent ductus arteriosus child - coarctation of the aorta	not specified not specified
		mother - coarctation of the aorta son - pulmonary valvular stenosis	not specified not specified
Howitt	1961	grandmother - atrial septal defect mother - atrial septal defect daughter - atrial septal defect	catheterization catheterization catheterization
Weil & Allenstein	1961	father - atrial septal defect daughter - atrial & ventricular septal defects son - atrial & ventricular septal defects plus pulmonic stenosis son - atrial septal defect & pulmonic stenosis daughter - atrial septal defect 2 daughters - ? atrial septal defect	surgery autopsy autopsy surgery catheterization clinical
Chelius et al	1962	father - coarctation of the aorta son - ventricular septal defect mother - atrial septal defect son - atrial septal defect and pulmonic stenosis daughter - tricuspid atresia child - tetralogy of Fallot	surgery catheterization catheterization surgery autopsy clinical
Zuckerman et al	1962	3 sisters - atrial septal defect son & daughter of #2 - atrial septal defect son & daughter of #3 - atrial septal defect	1. surgery 2. catheterization 3. clinical surgery in both catheterization in son surgery in daughter

CONTINUA EN OTRA

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Table 1 - continued

<u>AUTHOR</u>	<u>YEAR</u>	<u>RELATIONSHIP AND DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Christensen & Nelson	1963	2 sisters - ventricular septal defect	1. clinical
		2 children of #1 - ostium primum	2. autopsy
			2. autopsy
			clinical in both
Nadas	1963	father - patent ductus arteriosus	surgery
		4 children	
		1. aortic atresia	autopsy
		2. atrial septal defect, dextrocardia, patent ductus arteriosus	catheterization
Braunwald et al	1964	3. patent ductus arteriosus	surgery
		4. patent ductus arteriosus	clinical
		mother - patent ductus arteriosus	surgery
		daughter - patent ductus arteriosus	surgery
Robinson et al	1965	mother & 2 sons - idiopathic hypertrophic subaortic stenosis	catheterization in all
		father & daughter - idiopathic hypertrophic subaortic stenosis	autopsy
		mother & son - idiopathic hypertrophic subaortic stenosis	catheterization
		grandfather - pulmonary valve stenosis	in both
		grandson - pulmonary valve stenosis	catheterization
			autopsy

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Table 2
CONGENITAL HEART DEFECTS IN SIBLINGS
REVIEW OF THE LITERATURE

<u>AUTHOR</u>	<u>YEAR</u>	<u>DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Jewesbury	1912	patent ductus arteriosus in 2 sisters	clinical in both
Ellis	1936	patent ductus arteriosus in 2 sisters	clinical in both
Snelling	1937	patent ductus arteriosus in 2 sisters	clinical in both
Brown	1939	patent ductus arteriosus in 2 siblings in 2 different families	surgery in all
Weinberg & Himelfarb	1943	fibroelastosis in 2 siblings; 1 sibling also had coarctation of the aorta	autopsy in both
Kjaergaard	1946	patent ductus arteriosus in 3 sisters	clinical in all
Courtier et al	1948	atrial septal defect with congenital mitral stenosis (Lutembacher's syndrome) in 2 sisters	clinical in both
Jex-Blake	1948	ventricular septal defect in 2 sisters and a brother	clinical in all
Lamy & Schweisguth	1948	ventricular septal defect in 2 siblings in 2 different families	clinical in all
Campbell	1949	ventricular septal defect & pulmonic stenosis in 1 sibling; tetralogy of Fallot in another	catheterization clinical
Sorenson	1951	truncus arteriosus and ventricular septal defect in 1 sibling; transposition of the great vessels in another	autopsy autopsy

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STANDARD PLAN

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Table 2 - continued

<u>AUTHOR</u>	<u>YEAR</u>	<u>DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Sorenson (cont.)	1951	transposition of the great vessels in 1 sibling; tetralogy of Fallot in another	autopsy clinical
		biatrial cor triloculare and pulmonic stenosis in 1 sibling; atrial septal defect and pulmonic stenosis in another	autopsy catheterization
Coblentz & Mathivat	1952	pulmonic stenosis in 2 sisters	catheterization in both
McKeown et al	1953	transposition of the great vessels in 2 brothers	autopsy in both
		ventricular septal defect in 2 sisters	autopsy in both
		transposition of the great vessels and ventricular septal defect in a girl; patent ductus arteriosus in her brother	autopsy clinical
Record & McKeown	1953	patent ductus arteriosus in brother & sister	surgery in both
		patent ductus arteriosus in a boy; pulmonic stenosis in his sister	surgery in both
		truncus arteriosus with single ventricle in a girl; patent ductus in her sister	autopsy surgery
Anderson	1954	patent ductus arteriosus in a brother & sister	surgery in 1
		patent ductus arteriosus in 2 sisters	surgery in 1
		patent ductus arteriosus in a girl; patent ductus and coarctation in her sister	surgery in 1
Joyce & O'Toole	1954	patent ductus arteriosus in 3 brothers; a 4th brother has an undiagnosed cyanotic congenital heart lesion	surgery in both clinical

REPORT OF DISCUSSION

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Table 2 - continued

<u>AUTHOR</u>	<u>YEAR</u>	<u>DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Moss	1955	coarctation of the aorta in brother & sister	surgery in both
Kjellberg et al	1955	patent ductus arteriosus in 2 siblings	not specified
Polani & Campbell	1955	tetralogy of Fallot in 2 brothers	not specified
		tetralogy of Fallot in a girl; transposition of the great vessels in her sister	not specified
		tetralogy of Fallot in a boy; aortic stenosis in his brother & sister	not specified
Muller et al	1955	atrial septal defect in a brother & sister	surgery in both
Lamy et al	1957	tetralogy of Fallot in 2 siblings in 2 different families	not specified
		pulmonary valvular stenosis in 2 siblings	not specified
		ventricular septal defect in 2 siblings	not specified
		atrial septal defect in 2 siblings	not specified
		coarctation of the aorta in 2 siblings	not specified
		Eisenmenger's defect in 2 siblings	not specified
		pulmonary valvular stenosis in 1 sibling; tetralogy of Fallot in another	not specified
		atrial septal defect in 1 sibling; tetralogy of Fallot in another	not specified
		coarctation of the aorta in 1 sibling; tetralogy of Fallot in another	not specified

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Table 2 - continued

<u>AUTHOR</u>	<u>YEAR</u>	<u>DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Skelton & Coles	1958	atrial septal defect in 2 sisters	surgery in both
Carleton et al	1958	atrial septal defect in a girl; coarctation of the aorta in her brother	catheterization surgery
Campbell	1959	tetralogy of Fallot in 2 brothers	surgery clinical
		tetralogy of Fallot in a boy; pulmonic stenosis in his brother	clinical clinical
		pulmonary valvular stenosis and ventricular septal defect in a boy; tetralogy of Fallot in his brother	catheterization clinical
		pulmonary valvular stenosis in a girl; tetralogy of Fallot in her brother	catheterization surgery
		pulmonary valvular stenosis in a boy; tetralogy of Fallot in his brother	clinical clinical
		tetralogy of Fallot in a boy; aorticopulmonary window in his brother	autopsy clinical
		coarctation of the aorta in 2 sisters	surgery
		aortic stenosis in 2 brothers	surgery clinical
		aortic stenosis in 2 sisters	surgery clinical
		atrial septal defect with pulmonary valvular stenosis in 2 siblings	autopsy surgery

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CONCLUSION

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Table 2 - continued

<u>AUTHOR</u>	<u>YEAR</u>	<u>DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Campbell (cont.)	1959	ventricular septal defect with pulmonic stenosis in 2 siblings	catheterization clinical
		patent ductus arteriosus in 2 siblings in 2 different families	surgery in both
		patent ductus arteriosus in 2 brothers	autopsy surgery
Campbell	1960	patent ductus arteriosus in brother & sister	catheterization clinical
		patent ductus arteriosus in 2 sisters	surgery catheterization
		patent ductus arteriosus in brother & sister	surgery clinical
		patent ductus arteriosus in a girl; ventricular septal defect in her brother	surgery clinical
		patent ductus arteriosus in a boy; aortic stenosis in his sister (Turner's syndrome)	clinical autopsy
Campbell	1961	atrial septal defect in 2 sisters in 2 different families	surgery in both
Campbell & Polani	1961	coarctation of the aorta in 2 sisters	surgery in both
Chelius et al	1962	anomalous pulmonary venous drainage in a boy; ventricular septal defect in his brother	surgery surgery
		ventricular septal defect with patent ductus arteriosus in a girl; tetralogy of Fallot in her brother	surgery not specified

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Table 2 - continued

<u>AUTHOR</u>	<u>YEAR</u>	<u>DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Chelius et al (cont.)	1962	patent ductus arteriosus in brother & sister in 2 different families	surgery in both
		atrial septal defect in a boy; tetralogy of Fallot in his sister	catheterization autopsy
		atrial septal defect in a boy; aortic stenosis in his sister	clinical in both
		ventricular septal defect in brother & sister	catheterization in both
		tetralogy of Fallot in a girl; ventricular septal defect in her brother	surgery catheterization
		atrial septal defect with anomalous pulmonary venous drainage in 2 siblings	surgery in both
McKusick	1962	endocardial fibroelastosis in 2 siblings	autopsy in both
Vestermark	1962	endocardial fibroelastosis in 2 brothers	autopsy clinical
		endocardial fibroelastosis in brother and sister	autopsy in both
Christensen & Nelson	1963	atrial septal defect with pulmonary valvular stenosis in 2 sisters (niece by a normal sibling with atrial septal defect and pulmonary valvular stenosis; niece by a second sibling with ventricular septal defect)	surgery in both clinical surgery
		ostium primum defect in 2 sisters	surgery in both
		tetralogy of Fallot in 2 sisters; cyanotic congenital heart disease in a brother	surgery in both clinical

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Table 2 - continued

<u>AUTHOR</u>	<u>YEAR</u>	<u>DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
Christensen & Nelson (cont.)	1963	atrial septal defect in 2 siblings in 3 different families	catheterization and/or surgery in both
		ventricular septal defect in 2 siblings in 2 different families	catheterization and/or surgery in both
		pulmonary valvular stenosis in 2 siblings	catheterization surgery
Nadas	1963	tetralogy of Fallot in 2 siblings	catheterization surgery
		atrial septal defect in 2 siblings	not specified
		pulmonic stenosis in 2 siblings	not specified
		tetralogy of Fallot in 2 siblings	not specified
Braunwald et al	1964	idiopathic hypertrophic subaortic stenosis in 2 sisters and a brother	catheterization in all
		idiopathic hypertrophic subaortic stenosis in 2 brothers and a sister	catheterization in all
		idiopathic hypertrophic subaortic stenosis in 2 brothers	catheterization in both
		idiopathic hypertrophic subaortic stenosis in brother and sister	catheterization not specified
		idiopathic hypertrophic subaortic stenosis in 3 brothers	autopsy in 1 catheterization in 2
		idiopathic hypertrophic subaortic stenosis in 2 sisters	catheterization not specified

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<u>AUTHOR</u>	<u>YEAR</u>	<u>DIAGNOSIS</u>	<u>MEANS OF DIAGNOSIS</u>
McLoughlin et al	1964	tetralogy of Fallot in 1 brother; complete transposition of the great vessels, anomalies of venous return, etc. in his brother (both brothers had Laurence-Moon- Biedl-Bardet syndrome)	autopsy autopsy
Zoethout et al	1964	coarctation of the aorta with aortic stenosis in 2 sisters aortic stenosis in 2 siblings in 3 different families; (brother & sister in 2 families; 2 brothers in the third)	clinical surgery clinical in all

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DISCUSSION

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It is seen from Tables 1 and 2 that both similar and dissimilar lesions are found within single families. However, in the most striking pedigrees, i.e. several affected persons in more than one generation, the malformations tend to resemble each other. Furthermore, some of the apparently dissimilar defects have a common embryological background, so that both can be considered as errors of a single dynamic process. A case in point is that reported in Table 1 by Stein and Barber (1945) of a mother with a coarctation of the aorta who has two children with a patent ductus arteriosus. Both of these anomalies are related to improper development and reconstruction of the primitive aortic arches.

An additional manner in which apparently dissimilar lesions actually resemble each other is illustrated by the two siblings reported by Chelius, Rowe and Crumpton (1962) in Table 2. One child has the tetralogy of Fallot and the other a ventricular septal defect. Here it appears that the second child has a partial expression of the anomaly found in the first sibling.

There is a wide variation in the apparent modes of inheritance among the cases in Tables 1 and 2. In a few families the cardiac lesion appears to be a dominant trait, e.g. the atrial septal defect in a grandmother, mother and daughter reported by Campbell (1949), pulmonic valve stenosis in a mother and three children found by Lewis, Sonnenblick, Gilbert and Biber (1958), the father and six children with atrial septal defects described by Weil and Allenstein (1961) and the father and three children with patent ductus plus a fourth

It is seen from Tables I and A that both siblings and dissimilar lesions are found within single families. However, in the most striking pedigree, i.e. several affected persons in more than one generation, the affectional status to resemble each other. Furthermore, some of the apparently dissimilar defects have a common embryological background, so that both can be considered as errors of a single developmental process. A case in point is that reported in Table 2, in Stein and Gerson (1952) of a mother with a reconstruction of the aorta who has two children with a patent ductus arteriosus. Both of these anomalies are related to improper development and reconstruction of the primitive aortic arches.

An additional manner in which apparently dissimilar lesions actually resemble each other is illustrated by the two siblings reported by Chelios, Rose and Wangel (1952) in Table 2. One child has the constriction of aorta and the other a ventricular septal defect. Here it appears that the second child has a partial expression of the anomaly found in the first sibling.

There is a wide variation in the expression of the inheritance among the cases in Tables I and 2. In a few families the cardiac lesion appears to be a dominant trait, i.e. the aortic septal defect in a grandmother, mother and daughter reported by Campbell (1947), pulmonary valve stenosis in a mother and three children found by Lewis, Connors and Gerson (1950), the father and six children with aortic septal defects described by Wolf and Kirschstein (1951) and the father and three children with patent ductus arteriosus in a family

child with aortic atresia reported by Christensen and Nelson (1963). In other families the findings are consistent with the presence of a recessive gene of varying penetrance. There is no evidence for a sex-linked trait, since the defects are seen equally in males and females (Keith, Rowe and Vlad, 1958). In many cases, especially those in which only two members of the family are involved and the lesions are different in each, it is quite possible that the anomaly appeared by chance alone within closely related persons.

Two of the malformations found in Tables 1 and 2 are worthy of special comment. The first is subaortic stenosis. Familial aggregation of patients with this disorder has been observed on numerous occasions (Manchester, 1963; Brent, Akio, Fisher, Moran, Myers and Taylor, 1960). The question is, however, whether or not this defect can be considered congenital, since many affected persons apparently do not have subaortic stenosis until many years after birth. Like many diseases, there may be an inherited tendency for the development of the abnormality, but strictly speaking, the defect is not present at birth in many instances, and therefore is not congenital. A similar argument can be applied to endocardial fibroelastosis (Winter, Moses, Cohen and Naftalin, 1960; Vestermark, 1962). Again familial aggregation has been noted, although not so frequently as in subaortic stenosis, and again the lesion is not always present at birth.

A review of the literature concerning congenital heart defects in twins was recently presented by Rubenstein and Weaver (1965). They included only those cases in which there

which with genetic studies reported by Shostetman and Gellman (1953). In other families the findings are consistent with the presence of a recessive gene in varying penetrance. There is no evidence for a sex-linked trait, since the defects are seen equally in males and females (Gellman, Boye and Gellman, 1953). In many cases, especially those in which only two members of the family are involved and the lesions are different in each, it is quite possible that the anomaly appeared by chance alone within closely related persons.

Two of the malformations found in Tables I and II are worthy of special comment. The first is anodontia. Familial aggregation of patients with this anomaly has been observed on numerous occasions (Macpherson, 1953; Brown, 1953; Fisher, Moran, Wynn and Taylor, 1950). The question is, however, whether or not this defect can be considered congenital, since many affected persons apparently do not have anodontia until many years after birth. Like many diseases there may be an inherited tendency for the development of an abnormality, but strictly speaking, the defect is not present at birth in many instances, and therefore is not congenital. A similar argument can be applied to hereditary hypostomatia (Witter, Moses, Johns and Hattalin, 1950; Jernstrom, 1951). Again familial aggregation has been noted, although not so frequently as in anodontia, and again the lesion is not always present at birth.

A review of the literature concerning congenital heart defects is being presently completed by Jernstrom and Weaver (1955). They included only those cases in which there

was good documentation of monozygosity by appropriate study of the placenta, fingerprints, physical characteristics and/or blood groups. These cases are presented in Tables 3 and 4. Table 3 lists identical twins in which only one twin has a cardiac malformation; Table 4 shows a few cases in which both are affected.

If congenital heart defects are caused by genetic factors, one would expect to find the anomaly in both members of a monozygotic twinship. Sometimes this is the case as seen in Table 4. However, Table 3 contains numerous documented examples of identical twins in which only one has a demonstrable abnormality of the heart. This important fact must be taken into consideration when formulating any hypothesis regarding the etiology of congenital heart defects.

A number of studies have been conducted on large numbers of persons with congenital heart defects to determine if there were any common features which might have etiologic significance. The most extensive survey on the largest patient population to date was performed by Lamy, deGrouchy and Schweisguth (1957) in Paris. They divided their 1188 patients into eight diagnostic categories and investigated parental age at the birth of the propositus, consanguinity, prenatal disturbances, birth rank, sex distribution, and the familial incidence of cardiac deformities as well as congenital malformations in general. The same information was collected on 660 persons in the general population matched to the study group in "social and familial backgrounds, age of index cases, place of origin,

Table 3
SUMMARY OF DISCORDANT CONGENITAL HEART DEFECTS
IN PAIRS OF MONOZYGOTIC TWINS

Author & Date	Placenta	-----Diagnosis of Monozygosity-----			Lesion
		Physical Appearance	Finger- Prints	Blood Groups	
McClintock (1945)	+				Patent Ductus Arteriosus
Helweg-Larsen (1947)		+	+	+	Dextrocardia & Situs Inversus
Morison (1949)	+				DA, HLV, C (inf.), AV CB, EF
Forsyth (1951)	+	+	+	+	Atrial Septal Defect
Goldman (1952)	+	+	+	+	Atrial Septal Defect
Wade (1952)		+	+	+	Patent Ductus Arteriosus
		+	+	+	Pulmonic Stenosis
Lowe (1954)		+	+	+	Dextrocardia & Situs Inversus
Anderson (1954)		+		+	Patent Ductus Arteriosus
		+		+	Patent Ductus Arteriosus
Stadler (1955)	+	+			Dextrocardia
		+			Tetralogy of Fallot
Paes (1956)	+	+	+	+	Pseudotruncus Arteriosus
Uchida (1957)		+	+	+	Tetralogy of Fallot
		+	+	+	Tetralogy of Fallot
		+	+	+	Dextrocardia & Pulmonic Stenosis
		+	+	+	Ventricular Septal Defect
		+	+	+	Ventricular Septal Defect
		+	+	+	Ventricular Septal Defect
		+	+	+	Ventricular Septal Defect
		+	+	+	Ventricular Septal Defect
		+	+	+	Atrial Septal Defect
		+	+	+	Atrial Septal Defect
		+	+	+	Pulmonic Stenosis
		+	+	+	Pulmonic Stenosis
		+	+	+	Endocardial Fibroelastosis

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IN PATIENTS WITH CONGESTIVE HEART FAILURE
TREATMENT OF DISCREPANT CONCOMITANT HEART DEFECTS

Table 3 - continued

-----Diagnosis of Monozygosity-----				
Author & Date	Placenta	Physical Appearance	Finger-Prints	Blood Groups
				Lesion
Yuccoglu (1958)		+		+
				Tetralogy of Fallot and Atrial Septal Defect
Ross (1959)		+		+
				Tetralogy of Fallot
			+	+
			+	+
	+		+	+
	+		+	+
	+		+	+
	+	+		+
		Conjoined		+
	+		+	+
	+		+	+
	+		+	+
				Tetralogy of Fallot and Atrial Septal Defect
				Tetralogy of Fallot
				Pulmonic Stenosis
				Coarctation, Adult Type
				Ventricular Septal Defect
				Congenital Heart Disease, incompletely diagnosed
				Ventricular Septal Defect
				Cor Triloculare
				Ventricular Septal Defect
				Cured Endocardial Fibroelastosis
				Atrial Septal Defect

Key:

- AV = atrio-ventricular canal
- C (inf.) = coarctation of the aorta, infantile type
- CB = cor biloculare
- DA = dextroposition of the aorta
- EF = endocardial fibroelastosis
- HLV = hypoplasia of the left ventricle

Adapted from Rubenstein and Weaver (1965).

Memorandum - 1 sheet

Notes

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 3. Date 1961
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 5. Chapter 1
 6. Section 1
 7. Topic 1
 8. Subtopic 1
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Table 4
CONCORDANT HEART DEFECTS IN PAIRS OF MONOZYGOTIC TWINS

Author & Date	Placenta	Physical Appearance	Finger-Prints	Means of Proving Identity-----		Lesion A	Lesion B
				-----	Blood Groups		
Guistra (1939)	+					CB	CB
Kean (1942)		+				D	D + CHD
Benesove (1954)	+					TA + VSD	TA + VSD
Greaves (1954)			+		+	EF	EF
Ross (1959)	+	+			+	PDA	PDA
		+	+		+	VSD	ASD
Boulay (1961)		+			+	PDA	PDA

Key:

ASD = atrial septal defect
 CB = cor biloculare
 CHD = congenital heart defect
 D = dextrocardia
 EF = endocardial fibroelastosis
 PDA = patent ductus arteriosus
 TA = truncus arteriosus
 VSD = ventricular septal defect

Adapted from Rubenstein and Weaver (1965).

etc." They noted that while their patients came predominantly from Paris, the control group represented all of France, and they wondered if this difference might have affected their data, particularly the study of consanguinity, since the rate is known to be higher in Paris than in France as a whole.

Data for the study was collected by a combination of direct questioning, mailed questionnaires and a survey of medical records. Diagnosis of congenital defects in siblings was confirmed by clinical examination. Of note is that in 72.6% of their patients the cardiac diagnosis was established on clinical grounds with catheterization in "most" of this group; 14.3% were proven by surgery, and of the remaining 13.1% who were deceased at the time of the study, 61.9% had undergone post-mortem examination. From this information, it is impossible to determine the exact number of patients with proven diagnoses; perhaps about 60% had a definitive diagnostic procedure. However, 34% of Lamy's patients were classified as "Precise diagnosis has either not been possible or the defect was extremely complex."

The consanguinity rate was 3.6 times greater in the patient group as compared to the controls. Situs inversus, dextrocardia and common atrioventricular canal were the most frequent malformations in children resulting from these unions. The familial incidence of congenital anomalies of the heart and other organs was high in cases of consanguineous marriage. As noted earlier, however, a comparison of the differences be-

... This study was conducted in the ...
... from 1971, the overall mean age was ...
... they were ...
... the study of ...
... is known to be ...
... data for this study was ...
... direct observation, ...
... medical records, ...
... was confirmed by ...
... 72.6% of the ...
... on clinical grounds ...
... group; 11.3% ...
... 13.1% who were ...
... extensive post-mortem ...
... is impossible to ...
... given diagnosis; ...
... genetic procedures. ...
... that the "Practical ...
... defect was ...
... The ...
... that group the ...
... bacteremia and ...
... frequent ...
... The ...
... and other organs ...
... as noted ...

tween the patients and controls concerning consanguinity is not valid because of the selection of the controls.

Congenital heart defects were found in 1.46% of siblings of the index cases, and in none of the 1,483 siblings of the controls. The highest percent of affected siblings occurred in the patients with pulmonic valve stenosis, but the numbers are so small when the patients are divided into diagnostic categories that a significant difference cannot be determined. A list of the specific lesions found in the patients with affected siblings is included in Table 2. No cardiac defects were identified in the parents of either the study or control groups.

Polani and Campbell (1955) analyzed similar parameters on 377 patients in Great Britain. Most of their patients had a proven diagnosis, but the authors grouped their patients according to the presence or absence of cyanosis, so that it is impossible to compare their data for specific diagnostic categories with that obtained by others. It is known that a disproportionately high number of their patients had the tetralogy of Fallot (48%). The means of diagnosis in the affected siblings was not given, but the authors stated that it was "practically certain" that each had a cardiac defect even if the exact nature was not clear. Malformations of the heart were found in 1.42% of siblings. The mother of one patient was also affected. The consanguinity rate was no higher in the families of their patients than in a general hospital population they used as a standard.

tween the patients and controls regarding congenital

is not valid because of the selection of the controls.

Congenital heart defects were found in 1.4% of the

lings of the first group, and in none of the 1,447 children

of the controls. The highest percentage of affected children

occurred in the patients with pulmonary valve stenosis, 1.6%

the numbers are so small when the patients are divided into

diagnostic categories that a significant difference cannot

be determined. A list of the specific lesions found in the

patients with affected siblings is included in Table 1. In

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categories with that obtained by others. It is known that

disproportionately high number of their patients had the

tetralogy of Fallot (14%). The cause of cyanosis in the af-

ected siblings was not given, but the authors stated that it

was "practically certain" that each had a congenital defect, even

if the exact nature was not clear. Malformation of the heart

were found in 1.4% of siblings. The mother of one patient

was also affected. The corresponding rate was no higher in

the families of 313 patients than in a general hospital

population that was used as a standard.

Another British group, McKeown, MacMahon and Parsons (1953) also addressed the question of the incidence of congenital heart malformations in the families of 431 such patients. Precise diagnosis was established in about half of their patients and affected siblings. They investigated only siblings born after the propositus, and they found that 1.8% were affected. They also identified two parents with possible heart anomalies.

The only American studies of heart defects in the relatives of patients with cardiac malformations of all types have been presented by Neill and co-workers (Neill and Strang, 1960; Neill and Swanson, 1961). These papers have been published only in abstract so that the details of their materials and methods are unknown. It is known, however, that their patients came from widely scattered geographical locations, including many cases from other continents, so that it has been impossible for them to personally examine potentially affected family members. Neill and Strang (1960) found that 1.51% of the siblings of their 1,000 patients had a heart defect. The highest frequency of affected siblings occurred among the patients with dextrocardia. Identical lesions were found in over one half of the cases of multiple affected persons within a family. Two per cent of the index cases had a parent with a cardiac anomaly.

Neill and Swanson (1961) studied the 1,185 persons who attended the Harriet Lane Home Cardiac Clinic and

Another British group, Wessman, MacMillan and Pearson

(1955) also studied the question of the prevalence of congenital heart malformations in the families of 251 such patients. Precise diagnosis was established in about half of their patients and affected siblings. They investigated only siblings born after the diagnosis, and they found that 1.0% were affected. They also identified two patients with possible heart anomalies.

The only American studies of heart defects in the relatives of patients with cardiac malformations of all types have been presented by Hill and co-workers (Hill and Strang, 1960; Hill and Swanson, 1961). These papers have been published only in abstract so that the details of their materials and methods are unknown. It is known, however, that their patients came from widely scattered geographical locations, including many cases from other continents, so that it has been impossible for them to personally examine potentially affected family members. Hill and Strang (1960) found that 2.5% of the siblings of their 1,000 patients had a heart defect. The highest frequency of affected siblings occurred among the patients with tetralogy of Fallot. Identical lesions were found in over one half of the cases of multiple affected persons within a family. Two per cent of the index cases had a parent with a cardiac anomaly. Hill and Swanson (1961) studied the 1,187 persons who attended the Heart Institute Clinic during the

who had reached the age of 18 years. Questionnaires were sent to all, and 704 replied. Of these, 336 were married, and 235 had conceived. Of the live born offspring, 1.8% had congenital heart defects. Patients with a conotruncus malformation had the greatest incidence of cardiac and other malformations in their children. There was also a high spontaneous abortion rate in their cyanotic females.

Christensen and Nelson (1963) reviewed their records of patients with congenital heart defects undergoing cardiac catheterization. They identified 13 cases in which one or more sibling had a heart deformity, but they did not give the size of their patient population or the number of siblings at risk. One parent was also affected. The pedigrees of these families are given in Tables 1 and 2.

In addition to the above surveys of patients with heterogeneous forms of congenital heart anomalies, several papers have been published concerning the family history in patients with a specific cardiac diagnosis. Three such investigators originated in the United States; Anderson (1954) reviewed patients with patent ductus arteriosus, while Zoethout, Carter and Carter (1964) and Braunwald, Lambrew, Rockoff and Ross (1964) studied patients with aortic stenosis. The remainder were published abroad.

Record and McKeown (1953) investigated 166 persons with an isolated patent ductus arteriosus. Diagnosis was proven in about one half of these patients; 45 of those remaining

who had reached the age of 18 years. Questionnaires were sent to all, and 700 replied. Of these, 20 were excluded, and 235 had conceived. Of the 185 women of age 18 and over, 150 had congenital heart defects. Evidence with a congenital malformation had the greatest incidence of cardiac and other malformations in their children. There was also a high spontaneous abortion rate in their obstetric histories.

Christensen and Nelson (1967) reviewed their records of patients with congenital heart defects undergoing cardiac catheterization. They identified 13 cases in which one or more siblings had a heart deformity, but they did not give the size of their patient population or the manner of selection at risk. The parent was also affected. The histories of these families are given in Tables 1 and 2.

In addition to the above survey of patients with congenital forms of congenital heart anomalies, several papers have been published concerning the family history in patients with a specific cardiac diagnosis. These and investigators originated in the United States; Anderson (1964) reviewed patients with patent ductus arteriosus, while Fontana, et al. (1964) and Farrow (1964) and Fontana, et al. (1964) reviewed patients with aortic stenosis. The results were published separately.

Record and Nelson (1967) investigated 100 persons with an isolated patent ductus arteriosus. Diagnosis was based on about one half of these patients; 10 of these patients

were evaluated by private physicians employing a variety of unspecified diagnostic methods and were not seen by the authors. Family history data were collected by direct questioning and mailed questionnaires. They included only those siblings born after the proband and found that three of these 124 children (2.4%) had congenital heart defects confirmed by surgery or autopsy. The mother of one patient had had a patent ductus arteriosus ligated surgically. In reviewing the literature of case reports of two or more siblings afflicted with a patent ductus arteriosus, they observed that 23 of the 26 cases were female. This is an interesting exaggeration of the usual sex distribution in patent ductus of about 70% female.

Anderson (1954) studied 105 patients with an uncomplicated patent ductus, all of whom had undergone surgery. In 206 siblings, he found three with a patent ductus (1.4%); one also had a coarctation of the aorta. The author did not discuss the method of diagnosis in the siblings or the sex distribution. The data were collected primarily from questionnaires.

The third study of patients with a patent ductus arteriosus was performed by Polani and Campbell (1960) on 261 patients. The diagnosis was proven by surgery in 222, and in no case was there an associated cardiac anomaly. They found nine instances of congenital heart defects in an estimated 420 siblings (approximately 2%). Four of the nine affected siblings had a proven diagnosis, and six of the nine had a patent ductus. In only two of the cases were two sisters involved. One parent

were evaluated by private physicians employed a variety of unspecified diagnostic methods and were not seen by the authors. Family history data were obtained by direct questioning and mailed questionnaires. They included only those siblings born after the procedure and found that three of these 124 children (2.4%) had congenital heart defects confirmed by surgery or autopsy. The mother of one patient had had a patent ductus arteriosus ligated previously. In reviewing the literature of case reports of two or more siblings afflicted with a patent ductus arteriosus, they observed that 23 of the 26 cases were female. This is an interesting variation of the usual sex distribution in patent ductus arteriosus about 70% female.

Anderson (1954) studied 105 patients with patent ductus arteriosus, all of whom had undergone surgery. In 100 siblings, he found three with a patent ductus (3.0%). The method of diagnosis of the ductus was by direct examination. The data were collected primarily from cardiologists. The third study of patients with a patent ductus arteriosus was performed by Polani and Campbell (1960) on 107 patients. The diagnosis was proven by surgery in 125, and in 82 cases there an associated cardiac anomaly. They found nine instances of congenital heart defects in an estimated 100 siblings (approximately 9%). Four of the nine affected siblings had a proven diagnosis, and six of the nine had a recent cardiac only two of the cases were the subjects involved. The parents

had a possible pulmonic stenosis.

The same group of investigators has continued its interest in the family history and other background features of patients with heart defects and has published a series of studies on patients with different specific lesions. The next of these articles (Campbell and Polani, 1961a) concerned 170 patients with atrial septal defects. None of these patients had associated cardiac lesions "of consequence", and all but five had their defect proven by catheterization, surgery or autopsy. Almost all were of the secundum type. There were 378 siblings of these patients, and two had undergone surgery for an atrial septal defect. An additional two were thought to have a heart anomaly without a precise classification, giving a total prevalence of 1.1%. Four parents were thought to have an atrial septal defect, and this was proven in one case. Nineteen of the patients had offspring; two of their 23 children were thought to have a cardiac anomaly.

Campbell and Polani (1961b) reviewed 151 persons with coarctation of the aorta. Unlike the previous homogeneous groups, 30 of these patients had associated heart malformations. Six had aortic stenosis, seven had a patent ductus arteriosus, five had "major abnormalities of the branches of the aortic arch", three had congenital mitral insufficiency and two had pulmonic stenosis. In addition, there was one patient with each of the following: Eisenmenger's complex, transposition of the great vessels, the tetralogy of Fallot, tricuspid atresia, ventricular septal defect, mitral stenosis (congenital)

has a significant influence on the results.

The same group of investigators has also

interest in the study of the effect of the

of patients with heart disease and the

studies on patients with different degrees of

next of these studies (Graham, 1961) showed

170 patients with heart disease, some of whom

studies had associated cardiac disease, and

all the five had been given the same treatment,

every patient. (Graham, 1961) showed that

was the findings of these patients, and the

entirely for an entire year. In addition,

thought to have a heart disease which is

then, giving a total prevalence of 1.5%.

thought to have an actual heart disease, and

in one case, sixteen of the patients had

their 11 children were found to have a

Graham and Graham (1961) showed that

connection of the heart. In the

group, 10 of these patients had

five had cardiac stenosis, seven had a

five had cardiac stenosis, seven had a

study, which has been published in the

public domain. In addition, the

and of the following: (1) Graham, 1961;

of the heart, and (2) Graham, 1961;

studies, vascular disease, and (3) Graham,

and partial anomalous venous return. In this heterogeneous group it is difficult to evaluate possible etiologic factors pertaining specifically to coarctation of the aorta.

Nevertheless, they performed a questionnaire study of the 109 of their patients who had not been lost to follow-up. In 252 siblings, they found one case of a sister who had undergone surgical correction of a coarctation (0.4%). The mother of another patient had a patent ductus. Twenty-five of their patients had children of their own, and of these 41 offspring, one had pulmonary valvular stenosis. No mention is made of the documentation of the diagnosis in the mother or the offspring.

In 1962, Campbell published his series of 125 patients with pulmonic stenosis. The diagnosis was proven in 116. Again there was a large proportion of patients with associated defects; 15 had ventricular septal defects, six had atrial septal defects, two had coarctations, one had a large patent ductus arteriosus, one had a congenital aneurysm of a sinus of Valsalva and one had situs inversus. It would be interesting to know how many of these persons were included in more than one of the papers published by Campbell and associates!

The pulmonic stenosis patients had 282 siblings, and six of these (2.1%) had "certain" congenital heart defects. In addition there were two possibly affected siblings. No parent was found to have a heart anomaly. Thirteen offspring were observed in this group, and none had evidence of cardiac malformation.

and partial anomalous venous return. In this group it is difficult to establish a definite etiologic factor remaining especially to confirmation of the same.

Nevertheless, they performed a questionnaire where of the 100 of their patients who had not been lost to follow-up.

In 1933 findings, they found one case of a sister who had undergone surgical correction of a coarctation (6.4%). The mother of another patient had a patent ductus. Twenty-five of their patients had children of their own, and of these 15 offspring, one had pulmonary valvular stenosis. No correlation is made of the occurrence of the abnormality in the mother or the offspring.

In 1962, Campbell published his series of 100 patients with pulmonary stenosis. The diagnosis was proven in life. Again there was a large proportion of patients with associated defects; 14 had ventricular septal defects, 14 had atrial septal defects, 2 had coarctations, one had a large patent ductus arteriosus, one had a congenital aneurysm of a branch of Valsalva and one had aortic aneurysm. It would be interesting to know how many of these persons were included in one of the groups mentioned by Campbell and co-workers.

The pulmonary stenosis patients in the 1933 findings, and six of these (5.1%) had associated congenital heart defects. In addition there were two possibly related findings. No patient was found to have a bicuspid aortic valve. Abnormal offspring was observed in this group, and none had evidence of cardiac malformation.

The final paper from Campbell and others (Campbell and Goodwin, 1965) concerned 180 patients with ventricular septal defects unassociated with the tetralogy of Fallot. Diagnosis was proven in all but two cases, but 20 patients had additional cardiac malformations consisting of pulmonary stenosis, patent ductus arteriosus, atrial septal defect and aortic regurgitation. In some cases more than one of the above were present. Six of their 353 siblings (1.7%) were said to have congenital heart anomalies, although documentation was not discussed. No parents were affected.

Zoethout, Carter and Carter (1964) reported the family history in 126 patients with aortic stenosis. The diagnosis was proven in 36; it is not known whether these patients all had valvular aortic stenosis, or whether some had subvalvular or supra-valvular obstruction. The authors found seven possibly affected siblings out of 253 (2.8%). However, they calculated their figure at 4.0% by counting twice three families in which the two affected siblings were both seen in their clinic and therefore both were considered index cases. It does not seem reasonable to include two siblings as *propositi* in this kind of study, and so far as is known, this has not been done in any of the other reports. None of their patients had affected parents.

A series of 64 patients with a specific type of aortic stenosis, idiopathic hypertrophic subaortic stenosis, was reported by Braunwald, Lambrew, Rockoff, Ross and Morrow (1964). The diagnosis was proven in every case. Twenty-three of their

The final paper from Campbell and others (1960) and Goodwin (1967) concerned 130 patients with ventricular septal defects unassociated with the tetralogy of Fallot. Diagnosis was proven in all but two cases, but in patients had additional cardiac abnormalities consisting of pulmonary stenosis, patent ductus arteriosus, mitral regurgitation and aortic regurgitation. In some cases more than one of the above were present. Six of these 130 children (4.6%) were said to have congenital heart anomalies, although documentation was not obtained. No parents were affected. Goodwin, Carter and Carter (1964) reported the family history in 136 patients with aortic stenosis. The diagnosis was proven in 76; it is not known whether these patients all had valvular aortic stenosis, or whether some had subvalvular or supravalvular obstruction. The authors found seven possibly affected siblings out of 258 (2.7%). However, they calculated their figure at 4.0% by counting twice those families in which the two affected siblings were both sons. Their clinic and therefore both were considered index cases. It does not seem reasonable to include two siblings as positive in this kind of study, and so far as is known, this has not been done in any of the other reports. None of these patients had affected parents.

A series of 44 patients with a specific type of aortic stenosis, idiopathic aortic stenosis, was reported by Brannan, Lamborn, Bookoff, Ross and Morris (1964). The diagnosis was proven in every case. Twenty-eight of these

patients from 11 families had a relative with the same disorder, and the specific examples of affected parents and siblings are given in Tables 1 and 2. In seven of the 11 families with multiple affected persons, only siblings were definitely involved. The prevalence of idiopathic hypertrophic subaortic stenosis in relatives of patients with this disease cannot be calculated from the paper by Braunwald and associates since the size of the population at risk is not given. They suggested that when the disorder occurs in families, it is transmitted by an autosomal dominant mechanism.

Table 5 summarizes and compares the data from all the studies discussed above. It can be seen that the prevalence of affected siblings reported in the literature varies from the four per 1000 figure found in a group of patients with coarctation of the aorta to the rate of 28 per 1000 described in a series of patients with aortic stenosis. Obviously, however, the numbers are relatively small, and the methods of data collection not uniform, so that it is impossible to determine whether there is a significant difference.

To put these figures into perspective, it is necessary to examine the incidence of cardiac malformations in a general population. The most widely accepted rate is six cases of congenital cardiac malformations per 1000 live births as derived from the studies of Richards, Merritt, Samuels and Langmann (1955) and Carlgren (1959). The former is a prospective study of 6,053 infants born in a New York City hospital and examined at birth, six months and one year. An additional examination

patients from 11 families and a relative with the same condition, and the results are given in Table 1 and 2. In seven of the 11 families with multiple affected persons, only one person was definitely involved. The presence of idiopathic hypoadrenalism is in contrast to that of the familial form. This disease cannot be distinguished from the form of hypoadrenalism which is associated with the onset of the condition at birth. It is suggested that when the disease occurs in families, it is transmitted by an autosomal recessive mode.

Table 2 summarizes and compares the data from all the studies discussed above. It can be seen from the results of affected siblings reported in the literature that the rate per 1000 live births is a group of patients with hypoadrenalism of the order of 10 per 1000 live births. A series of patients with idiopathic hypoadrenalism, however, the numbers are relatively small, and the incidence of the disease is not uniform, so that it is impossible to determine whether there is a significant difference.

To put these figures into perspective, it is necessary to examine the incidence of certain malformations in a general population. The most widely accepted rate is six cases per 1000 live births (Wigglesworth, 1950). The incidence of hypoadrenalism from the studies of Wigglesworth, Wigglesworth and Wigglesworth (1955) and Wigglesworth (1959). The former is a population of 1,000 live births in a New York City hospital and the latter is a series of 1000 live births in an obstetric hospital at birth, six months and one year. An autosomal recessive

Table 5
A COMPARISON OF STUDIES OF ETIOLOGIC FACTORS
IN PATIENTS WITH CHD

	#* & Dx. of Pt.	CHD in Sibs/1000	CHD in Parents (# cases)	Consan.	Mat. Age	Distb. Preg.	Birth Rank	Seas. Birth
McKeown et al 1953	431 CHD	18	2	n.s.	n.s.	n.s.	n.s.	n.s.
Record & McKeown 1953	166 PDA	24	1	n.s.	o	+	+	+
Anderson 1954	205 PDA	14	0	o	n.s.	+	o	+
Polani & Campbell 1955	377 CHD	14.2	1	o	+	o	o	+
Lamy et al 1957	1188 CHD	14.6	0	+	o	+	+	n.s.
Polani & Campbell 1960	261 PDA	21	1	o	o	+	o	+
Neill & Strang 1960	1000 CHD	15.1	?	n.s.	n.s.	+	n.s.	n.s.
Campbell & Polani 1961	170 ASD	11	4	+	o	n.s.	o	o
Campbell & Polani 1961	151 coarc.	4	1	o	+	n.s.	o	+

Table 5 - continued

	# & Dx. of Pt.	CHD in Sibs/1000	CHD in Parents (# cases)	Consan.	Mat. Age	Distb. Preg.	Birth Rank	Seas. Birth
Campbell 1962	125 PS	21	0	0	0	n.s.	0	n.s.
Zoethout et al 1964	125 AS	28	0	0	0	0	0	0
Campbell & Goodwin 1965	180 VSD	17	0	n.s.	0	n.s.	n.s.	n.s.

Key:

- * - number of patients in study; in some papers only part
of the total patient population was used for individual sections.
+ - studied and found significant, or significance not evaluated.
o - studied - found not significant.
n.s. - not studied.
AS - aortic stenosis
ASD - atrial septal defect
CHD - congenital heart defects
COARC - coarctation of the aorta
PDA - patent ductus arteriosus
PS - pulmonic stenosis
VSD - ventricular septal defect

was performed at two years if doubt remained about the cardiac status. Of 4,515 live born infants living more than one month and either returning for both the six-month and one-year evaluation, or undergoing autopsy if deceased, 26 were found to have a cardiovascular malformation (6/1000). In 82 neonatal deaths, the incidence was 109/1000. If live born infants and neonatal deaths are tabulated together, the incidence of cardiovascular anomalies is 7.64/1000.

Carlgren (1959) attempted to identify all children with congenital heart defects born to mothers domiciled in the city of Gothenburg between 1941 and 1950. This was a retrospective study. He found 369 cases in 58,105 live births, an incidence of 6.4/1000.

A comparable rate was published by Kieffer, Adams, Anderson and Bearman (1959). They corresponded with all registered nurses in the state of Minnesota, inquiring about the presence of congenital cardiac defects in their offspring. Of 8,546 children, they found 4.4/1000 with proven lesions. If possible, cases were included, the rate became 5.4/1000.

Many other studies have produced a lower figure. In a prevalence study of heart anomalies in 156,775 children ranging in age from 0 to 15 years living in Toronto; Rose, Boyd and Ashton (1964) found a rate of 2.9/1000 live births. Gardiner and Keith (1951) performed a similar study on patients from the same cardiac registry, and reported a 2.1/1000 figure.

MacMahon, McKeown and Record (1953) studied the frequency of cardiac defects in the children of Birmingham, England and

was performed at two years of age. It was found that the prevalence of congenital heart defects in the city of Birmingham between 1941 and 1950 was 1.1/1000 live births. This was a retrospective study. He found 100 cases in 25,100 live births, an incidence of 4.4/1000.

Carls (1952) attempted to identify all children with congenital heart defects born to mothers residing in the city of Birmingham between 1941 and 1950. This was a retrospective study. He found 100 cases in 25,100 live births, an incidence of 4.4/1000.

A comparable rate was published by Steffen, Adams,

Anderson and Pearson (1952). They corresponded with all

registered nurses in the state of Minnesota, including about the prevalence of congenital heart defects in birth certificates.

Of 8,546 children, they found 4.4/1000 with congenital heart defects.

If possible, cases were included, the rate being 4.4/1000.

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Gardiner and Keith (1951) performed a similar study on patients

from the same cardiac registry, and reported a 2.1/1000 figure.

MacMahon, McIlroy and Morris (1953) studied the prevalence

of cardiac defects in the children of Birmingham, England and

derived a rate of 3.2/1000 live births. They used the same techniques as described for Carlgren (1959).

The rates quoted for the general population are presented graphically in Figure 1. The results of the several studies of siblings of patients with congenital heart defects are presented, as well, for comparison. It is seen that siblings are affected two to three times more often than expected, based on the best of the studies of the general population.

derived a name of 1,1,1,1-tetrafluoroethane. They used the name
tetrafluoroethane as described for CFC-114 (1971).
The name used for the central position is the
central position in the molecule. The number of the central
position of aliphatic compounds with unsaturated bonds, alkenes
are numbered, as well, for comparison. For example, 1,2-
alkenes are assigned to be more clear than 1,3-alkenes.
For the rest of the number of the central position
is also.

Figure 1

- 50 -

FREQUENCY OF CONGENITAL HEART DEFECTS

IN THE GENERAL
POPULATION:

Gardiner & Keith
Toronto 1951

MacMahon et al
Birmingham 1952

Richards et al
New York 1955

Carlgren
Gothenburg 1959

Rose et al
Toronto 1960

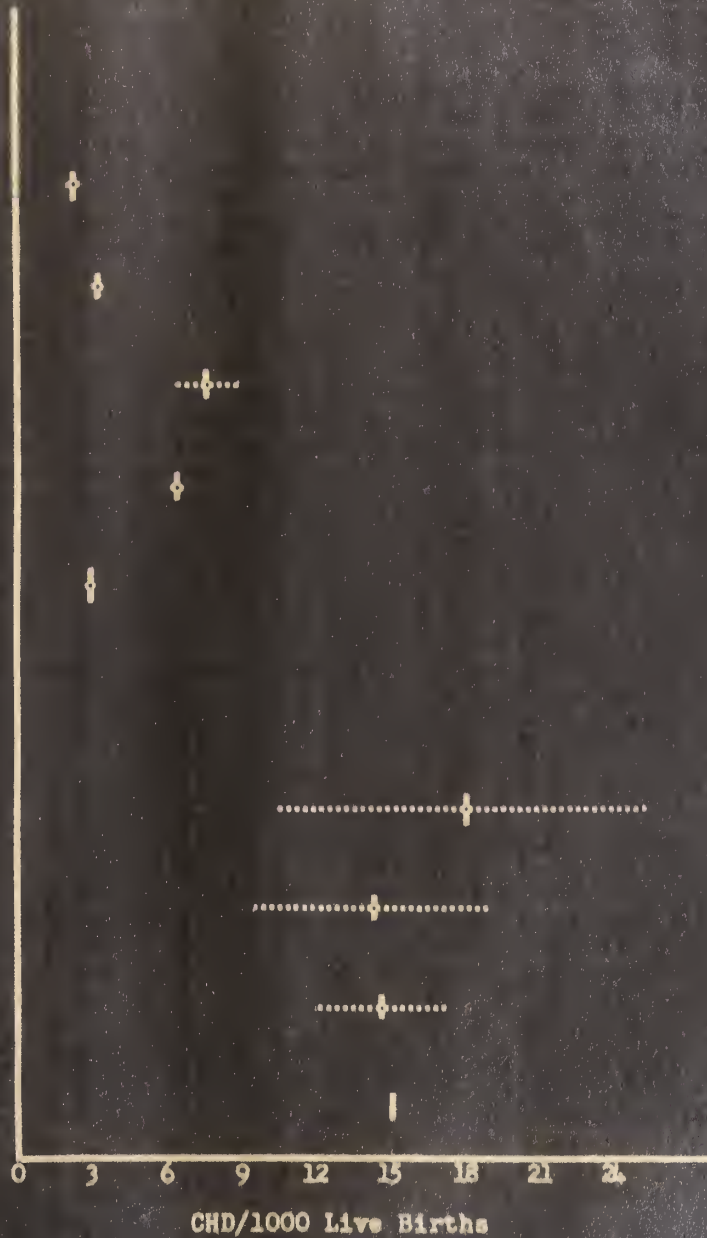
IN SIBLINGS OF
PTS. WITH CHD:

McKeown et al
1953

Polani & Campbell
1955

Lamy et al
1957

Neill & Strang
1960



..... One standard error around the rate

MATERIALS AND METHODS

The present study was undertaken in conjunction with a survey in the Department of Pediatrics of the 4,774 patients seen in the New Haven Rheumatic Fever and Cardiac Program Clinic (NHRF). This clinic was in existence for 13 years between 1947 and 1960, and was a demonstration pediatric cardiac clinic serving the children of the State of Connecticut. This clinic was under the auspices of the Connecticut State Department of Health, but was located within the Department of Pediatrics of the Yale University School of Medicine. Patients in need of hospitalization were generally admitted to the Grace-New Haven Community Hospital*, so that most of the catheterization, angiocardiography, surgery and autopsy data are from this hospital. The majority of patients current at the close of the demonstration clinic in 1960 have subsequently been followed in the pediatric, adolescent, and adult cardiac clinics of the Yale-New Haven Medical Center.

Of the 4,774 patients seen in the New Haven Rheumatic Fever and Cardiac Program Clinic, 44% were found to have congenital heart lesions, 39% had innocent murmurs, 13% had rheumatic heart disease and 4% had miscellaneous cardiac difficulties. All patients were divided into 100 subsamples, using a random sampling technique described by Tippet (1959). Data concerning the patient's history (family, social and medical,

*now the Yale-New Haven Medical Center

including prenatal events), selected points of the physical examination, laboratory findings, diagnosis, treatment and follow-up were coded and transferred to IBM cards. A copy of the code is in the appendix (Appendix A). Coding was performed by two medical students working independently, and it was checked by two pediatric cardiologists. Statistical agreement tests were run between the senior coders' results before the cards were punched and sorted. Diagnosis was recorded and coded according to Keith's Diagnostic Classification (Appendix B). The status of proof of the diagnosis was recorded as "possible", "probable", or "proven". In "proven" congenital heart defects patients, the diagnoses were established by catheterization, angiocardiography, surgery or autopsy, except for one case of coarctation of the aorta in which the diagnosis was considered "proven" by clinical findings alone. In some instances more than one of the above methods were employed. When more than one cardiac problem was manifest in a single patient, the person was classified according to the lesion felt to be the most significant. It should be noted that all patients except those lost to follow-up have had at least five years observation in the clinic, so that in most instances a "probable" diagnosis is the result of numerous examinations and laboratory studies.

Patients in the first 50 subsamples categorized as having a congenital heart defect (see Keith Code in Appendix B for details) were used for the present study. It was originally planned that the 677 patients in the same subsamples with

innocent murmurs could be used as a control group. However, a preliminary survey of 10% of the functional murmur patients demonstrated that many were referred to the clinic only because of concern stemming from the presence of organic heart disease in another member of the family. Thus, it was apparent that these patients could not serve as a control for such a study of the family history.

There were 767 patients in the congenital heart defects category in subsamples 1-50. Fifty of these were removed for one of the following reasons: 1) subsequent follow-up (to January, 1966) revealed that the suspected congenital heart lesion was either an innocent murmur or was rheumatic in origin; 2) duplication of single families within the series (two siblings in all cases); in such instances one sibling was removed; 3) adopted or foster children were not included because sufficient family history information could not be obtained. Table 6 gives the breakdown of the remaining 717 patients into diagnostic categories and shows the number of patients with "proven", "probable", and "possible" diagnoses.

There were a number of pertinent findings in the general survey of the 767 patients with congenital heart defects. No case of known consanguinity was identified, and the parental ages at the time of the patient's birth were not significantly different from those found in the innocent murmur patients. A high incidence of maternal bleeding during the first trimester was found in these patients, especially in those with cyanotic

Table 6
DISTRIBUTION OF PATIENTS BY DIAGNOSIS & STATE OF DIAGNOSIS

Keith Code #	Diagnosis	# Patients	% Male	% of Total Patients	-----# Proven	# Probable	-----# Possible
09	Aortic Stenosis	48	79	6.7	19	24	5
13	Atrial Septal Defect	120	38	6.7	47	58	15
23	Coarctation	35	51	4.9	30	5	0
44	Patent Ductus Arteriosus	98	28	13.7	86	9	3
54	Pulmonic Stenosis	63	57	8.8	43	19	1
59	Tetralogy of Fallot	63	56	8.8	59	4	0
61	Transposition	13	62	1.8	12	1	0
68	Ventricular Septal Defect	220	50	30.7	91	106	23
	Miscellaneous	<u>57</u>	<u>40</u>	<u>7.9</u>	<u>39</u>	<u>13</u>	<u>5</u>
	TOTAL	717	47.4	100.0	426	239	52

malformations. It should be remembered, however, that 50 patients were removed from the 767 cases in the general survey for the family history study, and therefore the exact figures from the general survey are not applicable to the present study. However, it is highly probable that the above findings would be found in the remaining 717 patients.

Within the 717 cases used for the family history study there were five instances in which the mother allegedly had rubella during the first trimester of pregnancy. In only one of these children were there any associated stigmata of the rubella syndrome. In none of the five cases was there a member of the family with a cardiac defect.

There were also 20 children with mongolism in the study. Their families were also free of heart malformations. As expected, 13 of these patients had atrial septal defects. The remainder were distributed between ventricular septal defects (3 cases), the tetralogy of Fallot (3 cases), and patent ductus arteriosus (1 case). It is realized that the patients with mongolism or a history of maternal rubella may have had their cardiac anomaly on a different etiologic basis than some of the other patients in the group. However, there are many other possibly important factors, as was seen in the review of the literature. To delete only these two particular groups of patients seemed rather arbitrary, and would have raised the prevalence of affected family members.

malformations. It should be remembered, however, that 50 patients were removed from the 100 cases in the general survey for the family history study, and therefore the exact figures from the general survey are not applicable to the present study. However, it is highly probable that the above findings would be found in the remaining 50 patients. Within the 100 cases used for the family history study there were five instances in which the mother slightly retarded during the first trimester of pregnancy. In only one of these children were there any associated signs of the rubella syndrome. In none of the five cases was there a member of the family with a cardiac defect. There were also 20 children with mongolism in the study. Their families were also free of heart malformations. As expected, 13 of these patients had aortic aortic defects. The remainder were distributed between ventricular septal defects (3 cases), the form of Vellie (2 cases), and patent ductus arteriosus (1 case). It is recalled that the patients with mongolism or a history of maternal rubella may have had their cardiac anomaly on a different etiologic basis than some of the other patients in the group. However, there are many other possibly important factors, as was seen in the review of the literature. To discuss only these two particular groups of patients seemed rather arbitrary, and would have raised the prevalence of affected family members.

Twenty patients in the study had twin siblings, of which 11 were non-identical. Identity was not proven by appropriate studies in any of the others. The distribution of the twins into the various diagnostic categories is shown in Table 7. There were no triplets among the patients.

To obtain current family history information, a questionnaire (Appendix C) was sent in 1965 to the parents of the patient population described above. It requested specific information concerning the number and ages of persons within the immediate family, and whether any had heart murmurs or heart disease. The immediate family was defined as parents, siblings and offspring. Half siblings were not included in the tabulations for prevalence statistics, although when one or more had a cardiac malformation, it was described for comparison with the patient's anomaly. Stillbirths and miscarriages were not tabulated, although neonatal deaths in siblings were counted.

Sixty-four per cent of the questionnaires were returned. In an additional 17%, there was no current address for the patient or his family; thus, 78% of the questionnaires received by the families were returned. These data are reviewed in Table 8. When no questionnaire was returned, the most recent information from the NHRF and Yale-New Haven charts was used. Family history data had been systematically obtained from all patients on admission to the New Haven Rheumatic Fever and Cardiac Program Clinic, so that there was reliable, even if outdated, information on every patient.

Twenty patients in the study had twin siblings, of which 11 were non-identical. Identical was not proven by appropriate studies in any of the others. The distribution of the twins into the various diagnostic categories is shown in Table 7. There were no differences among the patients. To obtain current family history information, a questionnaire (Appendix C) was sent in 1966 to the parents of the patient population described above. It requested specific information concerning the number and ages of persons within the immediate family, and whether any had heart murmurs or heart disease. The immediate family was defined as parents, siblings and offspring. Half siblings were included in the tabulations for purposes of statistical analysis, when one or more had a cardiac relationship. It was desirable for comparison with the patient's ancestry. Siblings and miscarriages were not tabulated, although potential siblings were counted.

Sixty-four per cent of the questionnaires were returned. In an additional 18, there was no return address for the patient or his family; thus, 70% of the questionnaires received by the families were returned. These data are reviewed in Table 8. When no questionnaire was returned, the most recent information from the MEX and Yale-New Haven hospitals was used. Family history data had been systematically obtained from all patients on admission to the Yale-New Haven Hospital since the Cardiac Program Clinic, so that there was reliability, even if outdated, information on every patient.

Table 7
DIAGNOSIS OF TWINS INCLUDED IN STUDY

Diagnosis	Number of Patients with a Twin
Aortic Stenosis	2
Atrial Septal Defect	2
Coarctation	0
Patent Ductus	3
Pulmonic Stenosis	3
Tetralogy of Fallot	3
Transposition	0
Ventricular Septal Defect	5
Miscellaneous	<u>2</u>
TOTAL	20

STATE OF NEW YORK OFFICE OF THE COMPTROLLER

FUND	DEPARTMENT
1	General
2	Agriculture
3	Education
4	Health
5	Justice
6	Labor
7	Military
8	Naval
9	Public Works
10	Railroads
11	Revenue
12	Veterinary
13	War
14	Water
15	Wildlife
16	Total

Table 8
RETURN OF QUESTIONNAIRES

Number sent	586	
Number not sent*	<u>121</u>	
	717	
<hr/>		
Number returned	457	
% of total		63.7
% of sent		78.0
Number not returned	<u>260**</u>	
TOTAL	717	

* Includes patients for which there is no recent address and those which were returned by the Post Office.

** Includes 46 patients who have been seen in the Yale-New Haven Hospital since 1960; in some instances complete family history information was present on the chart from the recent visit; thus, the number of patients on whom the family history is current is slightly greater than the number of returned questionnaires.

Table 2
STATUS OF QUESTIONS

Number not sent		Number sent	
246		246	
123		123	
123		123	
<hr/>		<hr/>	
Number returned		Number returned	
123		123	
123		123	
123		123	
<hr/>		<hr/>	
Number not returned		Number not returned	
123		123	
123		123	
123		123	
<hr/>		<hr/>	
TOTAL		TOTAL	
123		123	

* Includes patients for which there is no record address and those which were returned by the Post Office.

** Includes all patients who have been seen in the Yale-New Haven Hospital since 1900; in some instances complete family history information was present on the chart from the recent visit; thus, the number of patients on whom the family history is current is slightly greater than the number of returned questionnaires.

When any suggestion of a cardiac lesion was found either on a chart or in a returned questionnaire, it was investigated as fully as possible. In many cases the involved relative was already known in a cardiac clinic of the Yale-New Haven Medical Center, and these records were reviewed. When the involved person was deceased, medical and autopsy records were obtained whenever possible. Private physicians were contacted for information about suspected lesions, and they were very cooperative in providing the data requested. If the report from the doctor suggested a congenital heart malformation, or if there was no physician who could provide the necessary information, the affected person was asked to come in for a cardiac evaluation. A special clinic was established to examine such persons, and the patients were seen in consultation with two pediatric cardiologists, Dr. Ruth Whittemore and Dr. Shyamal Sanyal. Electrocardiograms, x-rays and phonocardiograms were obtained when appropriate. All living persons listed as affected in the tabulations except for one case of dextrocardia in a sibling, have been evaluated in the Yale-New Haven Medical Center, either in the special clinic set up for that purpose, or by regular appointment with a member of the cardiac staff. The one case of dextrocardia now lives out of state, and could not come to New Haven for evaluation. His diagnosis was proven by x-ray, although it is not certain whether or not there are associated anomalies.

When any suggestion of a further action was taken
on a case or in a technical question, it was investigated
as fully as possible. In many cases the medical records
were already known in a limited degree, and the
Medical Center, and other records were reviewed. When the
involved person was deceased, medical and dental records were
obtained whenever possible. Other records were
checked for information about suspected persons, and they were
very cooperative in providing the data required. Of the
reports from the doctor, suggesting a connection with the
case, or if there was no physician in the area, the
necessary information, the witness was not able to
in for a certain evaluation. A special effort was
made to examine each person, and the contacts were made in
connection with the medical records, and the
word and Dr. General Center. The information, and the
phonetic letters were obtained from the records. All
persons listed as affected in the investigation were
case of the person in a similar, and the records in the
Yale-New Haven Hospital, which, after the medical records
are up for that purpose, as the medical records of the
part of the medical staff. The case was determined
lives out of state, and could not be taken for
action. His diagnosis was given at the time, although it was
certain whether or not there was a connection.

The criteria for considering a diagnosis proven, probable, or possible in the living family members was the same as for the patients. Deceased patients not undergoing a complete post mortem examination were classified as having a probable diagnosis if the information received from the family, physician and/or hospital was consistent with the presence of a congenital heart defect. Where insufficient information was available, the diagnosis was considered as possible. Omitted altogether were undocumented references to siblings dying of unknown causes.

Chromosome analysis was undertaken on 11 persons from five families. These patients were selected for a preliminary survey because they either had multiple congenital anomalies, or there were multiple affected family members. It was felt that if positive results could be obtained, they would be most likely to appear in cases of this type. Patients were selected from the Pediatric Cardiac Clinic of the Yale-New Haven Medical Center, and they were not part of the present investigation of the family history in persons with congenital heart defects.

One of the patients selected because of the presence of multiple congenital anomalies including a heart malformation was a girl with a ventricular septal defect and pulmonic stenosis. At 13 years she had not shown any pubertal changes, and the remote possibility that she might have Turner's syndrome was considered. The other patient with multiple malformations was microcephalic, mentally retarded, and had unusual

The criteria for considering a diagnosis probable, possible, or probable in the family members was the same as for the patients. Disturbed patients not undergoing a complete post mortem examination were classified as uncertain a probable diagnosis if the information received from the family, physician and/or hospital was consistent with the presence of a congenital heart defect. When inconsistent information was available, the diagnosis was considered as possible. Omitted altogether were individuals with references to siblings dying of unknown causes.

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One of the patients selected because of the presence of multiple congenital anomalies including a heart malformation was a girl with a ventricular septal defect and pulmonary stenosis. At 13 years she had not shown any clinical symptoms and the remote possibility that she might have Turner's syndrome was considered. The other patient with multiple anomalies was microcephalic, mentally retarded, and had congenital

facial features consisting of an underdeveloped, low set right ear and a bizarre, uneven hairline. His cardiac diagnosis was also ventricular septal defect with pulmonary hypertension.

The families investigated included one in which four out of five siblings had proven obstruction in the left ventricular outflow tract. Lymphocytes from three of the affected children, the normal sibling and the mother were cultured. In the second family, a mother and daughter were investigated because of an atrial septal defect in the mother and a ventricular septal defect in the child. The mother's sister had a patent ductus arteriosus, and is included in the present family history study; she refused to come in for chromosome studies. In the third and last family study, there were unidentical twins in which one had a common atrioventricular canal; the other was thought at the time to have a ventricular septal defect. On subsequent examinations, however, her murmur was felt to be innocent.

Lymphocytes were cultured using a modification of the technique described by Moorhead, Nowell, Mellman, Batipps, and Hungerford (1960). The preparations were satisfactory for analysis in only six of the 11 persons. However, no abnormality could be demonstrated in any of the cells. In light of the repeated reports of normal karyotypes in persons with congenital heart defects, it was felt that the additional expense of repeating the poor cultures and extending the study was not warranted.

Physical features consisting of a prominent nose, right ear and a slight, uneven hairline. The cardiac shadow was also ventricularly shaped with pulmonary hypertension.

The families investigated included one in which four out of five siblings had proven obstruction in the left ventricular outflow tract. Lymphocytes from three of the affected children, the normal sibling and the mother were obtained. In the second family, a mother and daughter were investigated because of an arterial septal defect in the mother and a ventricular septal defect in the child. The mother's sister had a patent ductus arteriosus, and is included in the present family history study; she refused to have a lymphocyte study. In the third and last family study, there were identical twins in which one had a common atrioventricular canal; the other was thought at the time to have a ventricular septal defect. In subsequent examinations, however, her murmur was felt to be innocent.

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RESULTS

Siblings

A total of 1625 live-born, whole siblings were identified. Of these, 24 were diagnosed as having a congenital heart defect. Table 9 records the prevalence of affected siblings for patients in every diagnostic category. There were patients with affected siblings in every diagnostic group. The prevalence of siblings with cardiac anomalies for the over-all group was $1.48 \pm 0.30\%$. The highest rate was found in the patients with transposition of the great vessels, but the numbers were so small when patients were divided into diagnostic groups that statistical comparison was impossible.

The rate of affected siblings was lower when patients and affected siblings with only a "possible" diagnosis were excluded. Table 10 shows that the prevalence of siblings with "proven" or "probable" cardiac anomalies in patients with a "proven" or "probable" diagnosis was $1.28 \pm 0.29\%$. When only patients and affected siblings with a "proven" diagnosis were considered, the prevalence of siblings with congenital heart defects was $0.92 \pm 0.31\%$ (Table 11).

One reason for the variation in the rates of siblings with heart malformations when patients and affected siblings with different states of diagnosis are tabulated is demonstrated by Tables 12 and 13. All siblings were included in the over-all rate, but when a "proven" or "probable" diagnosis was required for inclusion, there were three possibly affected siblings of the patients under consideration who

RESULTS

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A total of 1625 live-born, whose siblings were identified. Of these, 24 were diagnosed as having a congenital heart defect. Table 9 records the prevalence of affected siblings for patients in every diagnostic category. There were patients with affected siblings in every diagnostic group. The prevalence of siblings with cardiac anomalies for the over-all group was 1.45% (0.30%). The highest rate was found in the patients with transposition of the great vessels, but the numbers were so small when patients were divided into diagnostic groups that statistical comparison was impossible. The rate of affected siblings was lower when patients and affected siblings with only a "possible" diagnosis were excluded. Table 10 shows that the prevalence of siblings with "proven" or "probable" cardiac anomalies in patients with a "proven" or "probable" diagnosis was 1.24% (0.52%). When only patients and affected siblings with a "proven" diagnosis were considered, the prevalence of siblings with congenital heart defects was 0.92% (0.31%) (Table 11).

One reason for the variation in the rate of siblings with heart malformations when patients and affected siblings with different states of diagnosis are tabulated is demonstrated by Tables 12 and 13. All siblings were included in the over-all rate, but when a "proven" or "probable" diagnosis was required for inclusion, there were three possible affected siblings of the patients under consideration and

Table 9
FREQUENCY OF CONGENITAL HEART DEFECTS
IN SIBLINGS OF ALL PROPOSITI

<u>Diagnosis of Patient</u>	<u># Pts.</u>	<u># Sibs</u>	<u># Affected Sibs</u>	<u>%</u>	<u>S.E.</u>
Aortic Stenosis	48	104	1	0.96	0.96
Atrial Septal Defect	120	302	3	0.99	0.57
Coarctation	35	85	2	2.35	1.67
Patent Ductus Arteriosus	98	245	3	1.22	0.71
Pulmonic Stenosis	63	134	3	2.23	1.29
Tetralogy of Fallot	63	140	2	1.42	1.00
Transposition	13	33	1	3.03	3.03
Ventricular Septal Defect	220	468	8	1.72	0.61
Miscellaneous	<u>57</u>	<u>114</u>	<u>1</u>	<u>0.88</u>	<u>0.88</u>
TOTAL	717	1625	24	1.48	0.30

Key:

S.E. - standard error

(S.E. = r / \sqrt{n} ; r = rate, n = number on which the rate is based)

TABLE 2
PERCENTAGE OF CHRONICALLY ILL PATIENTS
IN CLINICAL STUDY

Age	Sex	Duration of Illness (Years)	Chronic Illness (%)	Acute Illness (%)	Diagnosis of Patient
10.0	M	1	100	100	Chronic Illness
12.0	F	1	100	100	Chronic Illness
14.0	M	1	100	100	Chronic Illness
16.0	F	1	100	100	Chronic Illness
18.0	M	1	100	100	Chronic Illness
20.0	F	1	100	100	Chronic Illness
22.0	M	1	100	100	Chronic Illness
24.0	F	1	100	100	Chronic Illness
26.0	M	1	100	100	Chronic Illness
28.0	F	1	100	100	Chronic Illness
30.0	M	1	100	100	Chronic Illness
32.0	F	1	100	100	Chronic Illness
34.0	M	1	100	100	Chronic Illness
36.0	F	1	100	100	Chronic Illness
38.0	M	1	100	100	Chronic Illness
40.0	F	1	100	100	Chronic Illness
42.0	M	1	100	100	Chronic Illness
44.0	F	1	100	100	Chronic Illness
46.0	M	1	100	100	Chronic Illness
48.0	F	1	100	100	Chronic Illness
50.0	M	1	100	100	Chronic Illness
52.0	F	1	100	100	Chronic Illness
54.0	M	1	100	100	Chronic Illness
56.0	F	1	100	100	Chronic Illness
58.0	M	1	100	100	Chronic Illness
60.0	F	1	100	100	Chronic Illness
62.0	M	1	100	100	Chronic Illness
64.0	F	1	100	100	Chronic Illness
66.0	M	1	100	100	Chronic Illness
68.0	F	1	100	100	Chronic Illness
70.0	M	1	100	100	Chronic Illness
72.0	F	1	100	100	Chronic Illness
74.0	M	1	100	100	Chronic Illness
76.0	F	1	100	100	Chronic Illness
78.0	M	1	100	100	Chronic Illness
80.0	F	1	100	100	Chronic Illness
82.0	M	1	100	100	Chronic Illness
84.0	F	1	100	100	Chronic Illness
86.0	M	1	100	100	Chronic Illness
88.0	F	1	100	100	Chronic Illness
90.0	M	1	100	100	Chronic Illness
92.0	F	1	100	100	Chronic Illness
94.0	M	1	100	100	Chronic Illness
96.0	F	1	100	100	Chronic Illness
98.0	M	1	100	100	Chronic Illness
100.0	F	1	100	100	Chronic Illness

Key:

1.0 - standard error

(1.0 - 2.0) = 1.0
the data in parentheses

Table 10
FREQUENCY OF CHD IN SIBLINGS OF PROPOSITI: DIAGNOSIS
PROVEN OR PROBABLE IN BOTH PATIENT AND AFFECTED SIB

<u>Diagnosis of Patient</u>	<u># Pts.</u>	<u># Sibs</u>	<u># Sibs CHD</u>	<u>% Sibs CHD</u>	<u>S.E.</u>
Aortic Stenosis	43	81	1	1.234	1.23
Atrial Septal Defect	105	262	1	0.381	0.38
Coarctation	35	85	2	2.352	1.66
Patent Ductus Arteriosus	95	239	3	1.255	0.72
Pulmonic Stenosis	62	128	2	1.562	1.10
Tetralogy of Fallot	63	140	2	1.43	1.00
Transposition	13	33	1	3.03	3.03
Ventricular Septal Defect	197	408	6	1.470	0.59
Miscellaneous	<u>52</u>	<u>110</u>	<u>1</u>	<u>0.909</u>	<u>0.91</u>
TOTAL	665	1486	19	1.28	0.29

S.E. = standard error = r/\sqrt{n}
 r = rate
 n = number on which rate is based

Table 10
FREQUENCY OF CHD IN SIMILAR TO COMPLEXITY: DIAGNOSTIC
PROVEN OR PROBABLE IN BOTH PATIENT AND ALBINO

Diagnosis of Patient	N	%	95% CI	95% CI
Aortic Stenosis	13	81	0	1.21
Atrial Septal Defect	107	262	1	0.14
Coarctation	32	82	2	0.60
Patent Ductus Arteriosus	92	238	3	0.75
Pulmonic Stenosis	62	133	2	1.12
Tetralogy of Fallot	63	140	3	1.00
Transposition	13	32	1	0.10
Ventricular Septal Defect	107	408	4	0.30
Miscellaneous	32	110	1	0.09
TOTAL	562	1440	19	1.20

1.21 = standard error = $\sqrt{1/n}$
 n = number on which rate is based
 r = rate

Table 11
FREQUENCY OF CHD IN SIBLINGS OF PROPOSITI: DIAGNOSIS
PROVEN IN BOTH PATIENT AND AFFECTED SIBLING

<u>Diagnosis of Patient</u>	<u># Pts.</u>	<u># Sibs</u>	<u># Sibs CHD</u>	<u>% Sibs CHD</u>	<u>S.E.</u>
Aortic Stenosis	19	35	0	0.0	0.0
Atrial Septal Defect	47	122	1	0.82	0.82
Coarctation	30	80	1	1.25	1.25
Patent Ductus Arteriosus	86	212	3	1.42	0.82
Pulmonic Stenosis	43	86	1	2.70	2.70
Tetralogy of Fallot	59	129	0	0.00	0.00
Transposition	12	32	1	3.13	3.13
Ventricular Septal Defect	91	191	1	0.52	0.52
Miscellaneous	<u>39</u>	<u>93</u>	<u>1</u>	<u>1.08</u>	<u>1.08</u>
TOTAL	426	980	9	0.92	0.31

S.E. = standard error = r/\sqrt{n}
 r = rate
 n = number on which rate is based

Table 11
FREQUENCY OF CNO IN SIBLINGS OF PROBABLY BLENDED
FOLLOWS IN BOTH PATIENT AND AFFECTED SIBLING

Diagnosis of Patient	# Sibs	# Sibs CNO	# Sibs CNO	S.E.
Aortic Stenosis	19	35	0	0.0
Atrial Septal Defect	47	122	1	0.02
Coarctation	30	80	1	0.02
Patent Ductus Arteriosus	86	212	3	0.03
Pulmonic Stenosis	43	86	1	0.01
Tetralogy of Fallot	29	129	0	0.00
Transposition	12	32	1	0.13
Ventricular Septal Defect	91	191	2	0.02
Miscellaneous	22	92	1	0.06
TOTAL	126	980	9	0.02

S.E. = standard error = $\sqrt{\frac{r}{n}}$
r = rate
n = number on which rate is based

Table 12
STATE OF DIAGNOSIS IN PATIENTS AND AFFECTED SIBLINGS

State of Dx. in Patient	# Pts.	# Sibs	-----Affected Siblings-----		
			# Sibs with Proven Dx.	# Sibs with Probable Dx.	# Sibs with Possible Dx.
Proven	426	980	9	4	2
		*		
Probable	239	506	3	3	1
			-----	-----	**
Possible	52	139	1	1	0
			-----	-----	***
TOTAL	717	1625	13	8	3

* 9 siblings with "proven" CHD out of 980. See #3 in Table 13.

** 12 siblings with "proven" CHD (9+3) and 7 with "probable" CHD (4+3), making a total of 19 affected siblings with a "proven" or "probable" diagnosis out of 1486 (980+506). See #2 in Table 13.

*** 13 siblings with "proven" CHD (9+3+1), 8 with "probable" CHD (4+3+1) and 3 with "possible" CHD (2+1+0), making a total of 24 affected siblings out of 1625. See #1 in Table 13.

SECRET

Table 13
PREVALENCE OF CHD IN THE SIBLINGS
OF PATIENTS WITH CHD

<u>State of Dx. (Pt.& Aff.Sib.)</u>	<u># Pts.</u>	<u>CHD in Sibs/ # Sibs</u>	<u>Rate/1000 Live Born Sibs</u>	<u>S.E.</u>
1. Proven + Probable + Possible	717	24/1625	14.8	3.02
2. Proven + Probable	665	19/1486	12.8	2.93
3. Proven	426	9/980	9.2	3.07

Table 13
 PERCENTAGE OF CHD IN THIS RACE
 BY PATIENTS WITH CHD

State of D.C. (P.C. & A.P. & S.D.)	% Per.	CHD in 1945 in 1945	CHD in 1945 in 1945
1. Proven + Probable + Possible	71%	22,100	10.0
2. Proven + Probable	63%	19,700	11.5
3. Proven	49%	9,700	8.2

were counted as normal. Likewise, when only patients and affected siblings with "proven" diagnoses were investigated, there were six potentially affected siblings considered as normal because their diagnosis was either "probable" or "possible".

The specific cases in which a sibling of a patient had a cardiac defect are listed in Table 14. The lesions in both patient and sibling were identical in 13 of the 24 cases, although in six there were one or more additional cardiac anomalies in the patient or sibling. Such a situation was termed "partial identity" and is exemplified by case M.T. The patient had an isolated ostium primum defect; her sibling had the same type of atrial septal defect and also had pulmonic stenosis. The anomalies were thought to be entirely different in seven cases, and in four additional instances, the nature of the defect in the sibling was unknown. In none of the twins was the twin sibling affected.

Parents

In five patients there was evidence of a cardiac anomaly in a parent. These cases are detailed in Table 15. Of particular interest was that the lesions were identical or partially identical in all instances.

In two families (R.M. and J.C.) both a sibling and a parent were affected. Aortic stenosis was present in the father, and two children (including the patient) in one family and in the other, the mother and two children had pulmonic stenosis.

The rate of affected parents is calculated from the total number of parents (1434) and is $0.35\% \pm 0.15\%$.

were counted as normal. Likewise, when only affected and affected siblings with "proven" diagnosis were considered, there were six potentially affected siblings considered as normal because their diagnosis was either "probable" or "possible".

The specific cases in which a sibling of a patient has a cardiac defect are listed in Table 15. The lesions in both patient and sibling were identical in 13 of the 26 cases, although in six there were one or more additional cardiac anomalies in the patient or sibling. Such a situation was termed "partial identity" and is illustrated in case M.T. The patient had an isolated aortic bicuspid valve, her sibling had the same type of aortic aortic valve and also had pulmonary stenosis. The anomalies were shared by no more than two siblings in seven cases, and in four additional instances, the nature of the defect in the sibling was unknown. In none of the twins was the twin sibling affected.

Parents

In five patients there was evidence of a cardiac anomaly in a parent. These cases are listed in Table 15. Of particular interest was that the lesions were identical or partially identical in all instances. In two families (P.H. and J.O.) both a sibling and a parent were affected. Aortic stenosis was present in the parent and two children (including the patient) in one family and in the other, the mother and two children had pulmonary stenosis. The rate of affected parent is estimated to be 1.5% total number of parents (15) and is 0.75% (2.1%).

Table 14
CONGENITAL HEART DEFECTS IN PROPOSITI
AND THEIR AFFECTED SIBLINGS

<u>Case</u>	<u>Dx. & State of Patient</u>	<u>Sex</u>	<u># of Sibs</u>	<u>Dx. & State of Affected Sib.</u>	<u>Sex</u>
(1)					
R.M.	Probable Aortic Stenosis	M	2 ⁽²⁾	Probable Aortic Stenosis	M
M.T.	Proven ASD (ostium primum)	M	3	Proven ASD + Pulmonic Stenosis (ostium primum)	F
V.D.	Proven ASD	F	3	Possible CHD ⁽³⁾	?
A.G.	Probable ASD	F	5	Possible CHD ⁽⁴⁾	M
R.T.	Proven Coarc. + Aortic Stenosis	F	2	Proven ASD	F
R.K.	Probable Coarc. + Aortic Stenosis	M	3	Proven Coarc., PDA, + Endocardial Fibroelas- tosis	F
M.P.	Proven PDA	F	2	Proven PDA	F
L.C.	Proven PDA	F	8	Proven ASD ⁽⁵⁾	F
N.C.	Proven PDA + Left SVC	F	5	Proven Tetralogy of Fallot	F
J.W.	Proven Pulmonic Stenosis + ASD	F	6	Proven VSD	F
G.D.	Proven Pulmonic Stenosis	F	2	Possible CHD ⁽⁶⁾	F
(7)					
J.C.	Probable Pulmonic Stenosis	M	1	Probable Pulmonic Stenosis	F

Table 14 - continued

<u>Case</u>	<u>Dx. & State of Patient</u>	<u>Sex</u>	<u># of Sibs</u>	<u>Dx. & State of Affected Sib.</u>	<u>Sex</u>
S.D.	Proven Tetralogy of Fallot + Cong. Aortic Insuff.	F	1	Probable CHD (8)	F
S.P.	Proven Tetralogy of Fallot	F	1 (9)	Probable Truncus Arteriosus	M
R.S.	Transposition + Proven Pulmonic Stenosis	M	4	Proven VSD + ? (10)	M
L.A.	Proven VSD	F	2	Proven VSD, Coarc. + PDA	M
T.H.	Proven VSD	F	3	Probable VSD	F
S.S.	Proven VSD	M	2	Probable VSD	M
A.B.	Probable VSD	M	1	Proven Endocardial Cushion Defect, Over-riding aorta, Sten. of R & L Pul. Art.	M
D.O.	Probable VSD	M	2	Probable VSD	M
M.L.	Probable VSD	F	2	Proven LVH with outflow obstruction	M
D.H.	Possible VSD	F	5	Proven Endocardial Fibroelastosis	M
S.Y.	Possible VSD	F	1	Probable VSD	M
T.D.	Proven Dextrocardia, ASD, Anom. Venous Return	M	7	Proven Dextrocardia	M

Attendance - 11 May

No.	To attend & to be received	No. of days	No.	Total & to be received	Total
1	(1) 1000000000	1	1	Violence & to be received	1000
2	1000000000	1	1	Violence & to be received	1000
3	1000000000	1	1	Violence & to be received	1000
4	1000000000	1	1	Violence & to be received	1000
5	1000000000	1	1	Violence & to be received	1000
6	1000000000	1	1	Violence & to be received	1000
7	1000000000	1	1	Violence & to be received	1000
8	1000000000	1	1	Violence & to be received	1000
9	1000000000	1	1	Violence & to be received	1000
10	1000000000	1	1	Violence & to be received	1000

Table 14 - continued

Key:

1. Father had possible aortic stenosis; see Table 16.
2. A second sibling, age 14 years, has a murmur with functional characteristics which has been present since age 1 month. Normal EKG. ? organic.
3. Cyanotic; died at age 3 days; no other information.
4. Died at 2 months as a "blue baby". No other information.
5. This woman's daughter had a ventricular septal defect.
6. Died at 1 day of age. Autopsy showed enlarged heart with "left ventricular hypertrophy."
7. Mother had proven pulmonic stenosis. See Table 16.
8. Died at 15 months; cyanotic and said to have CHD. no autopsy.
9. Two half siblings (common father) were cyanotic and said to have congenital heart defects. Both died as school children more than 20 years ago; no medical records.
10. Died at 6 weeks with cyanotic CHD. Autopsy showed ventricular septal defect, but no mention was made of origin of great vessel. Clinically it was felt that the sibling had a transposition.

ASD = atrial septal defect
LVH = left ventricular hypertrophy
PDA = patent ductus arteriosus
SVC = superior vena cava
VSD = ventricular septal defect

Table 1A - continued

Key:

1. Father had possible aortic stenosis; see Table 1B.
2. A second sibling, age 14 years, has a murmur with functional characteristics which has been present since age 1 month. Normal EKG. 3 cyanotic.
3. Cyanotic; died at age 3 days; no other information.
4. Died at 2 months as a "blue baby". No other information.
5. This woman's daughter had a ventricular septal defect.
6. Died at 1 day of age. Autopsy showed enlarged heart with "left ventricular hypertrophy."
7. Mother had proven pulmonary stenosis. See Table 1B.
8. Died at 15 months; cyanotic and still alive EKG. no autopsy.
9. Two half siblings (common father) were cyanotic and said to have congenital heart defects. Both died as school children more than 20 years ago; no medical records.
10. Died at 6 weeks with cyanotic EKG. Autopsy showed ventricular septal defect, but no mention was made of origin of great vessel. Clinically it was felt that the sibling had a transposition.

ASD = atrial septal defect
 LVH = left ventricular hypertrophy
 PDA = patent ductus arteriosus
 SVC = superior vena cava
 VSD = ventricular septal defect

Table 15
CONGENITAL HEART DEFECTS IN THE PARENTS OF PROPOSITI

<u>Case</u>	<u>Dx. & State of Patient</u>	<u>Sex</u>	<u>Dx. & State of Parent</u>	<u>Relation- Ship</u>
R.M. ⁽¹⁾	Probable Aortic Stenosis	M	Possible Aortic Stenosis	Father
J.M.	Proven Valvular Aortic Stenosis	M	Proven Idiopathic ⁽²⁾ Left Ventricu- lar Hypertrophy	Father
P.S.	Proven Patent Ductus Arteriosus	F	Probable Patent Ductus Arteriosus	Mother
C.T.	Proven PDA + VSD	F	Probable VSD	Father
J.C. ⁽³⁾	Probable Pulmonic Stenosis	M	Proven Pulmonic Stenosis	Mother

-
1. Sibling of patient also had aortic stenosis; see Table 15.
 2. Died suddenly at age 38. Autopsy showed marked left ventricular hypertrophy. On microscopic examination, findings were consistent with idiopathic hypertrophic subaortic stenosis. Two siblings in this family have murmurs with characteristics of an innocent murmur. Organic ?
 3. Sibling of patient also had pulmonic stenosis; see Table 15.

Table 15
CONGENITAL HEART DEFECTS IN THE FAMILIES OF PROSPERITY

Case	No. of Patients	Sex	No. of Patients	Relation to Ship
R.M. (1)	Probably Aortic Stenosis	M	Possible Aortic Stenosis	Uncertain
J.M.	Proven Valvular Aortic Stenosis	M	Proven Idiopathic Left Ventricular Hypertrophy	Uncertain (2)
P.S.	Proven Patent Ductus Arteriosus	F	Probably Patent Ductus Arteriosus	Uncertain
G.T.	Proven PDA + VSD	F	Probably VSD	Uncertain
J.C. (3)	Probably Pulmonic Stenosis	M	Proven Pulmonic Stenosis	Uncertain

1. Sibling of patient also had aortic stenosis; see Table 15.

2. Died suddenly at age 35. Autopsy showed marked left ventricular hypertrophy. On microscopic examination, findings were consistent with idiopathic hypertrophic subaortic stenosis. Two siblings in this family have mitral valve stenosis characteristic of an innocent murmur. (Grandfather)

3. Sibling of patient also had pulmonic stenosis; see Table 15.

Offspring

Of the 717 patients, 250 are believed to have lived past the age of 18 years. However, current family history information was available on only 160. Of these, 41 have had a total of 77 offspring. Two of the offspring have a congenital heart defect, as shown in Table 16. Thus, the prevalence of affected offspring is $2.6 \pm 1.84\%$. The lesion was the same in patient and child in one case and probably different in the other (the second patient with an affected offspring has not been seen for many years; conceivably her diagnosis could change on re-evaluation).

Patients in each diagnostic category except transposition of the great vessels have been observed to have offspring.

Offspring

Of the 717 patients, 351 are believed to have lived past the age of 15 years. However, certain family history information was available on only 160. Of these, 41 have had a total of 77 offspring. Two of the offspring have a congenital heart defect, as shown in Table 1. Thus, the prevalence of affected offspring is 2.61%. The incidence was the same in patient and child in one case and probably different in the other (the second patient with an affected offspring has not been seen for many years; conceivably her diagnosis could change on re-evaluation).

Patients in each diagnostic category except for most-
tion of the great vessels have been observed to have off-
spring.

Table 16
OFFSPRING OF PATIENTS

<u>Diagnosis of Patient</u>	<u>Sex</u>	<u># with Offspring</u>	<u># Offspring</u>	<u># Offspring with CHD</u>
Aortic Stenosis	M	3	6	0
	F	0	0	0
Atrial Septal Defect	M	1	1	0
	F	7	12	1 (VSD)
Coarctation	M	3	6	0
	F	3	5	0
Patent Ductus Arteriosus	M	1	2	0
	F	8	16	1 (PDA + VSD)
Pulmonic Stenosis	M	1	1	
	F	2	3	0
Tetralogy of Fallot	M	1	2	0
	F	1	2	0
Transposition	M	0	0	0
	F	0	0	0
Ventricular Septal Defect	M	5	11	0
	F	<u>5</u>	<u>10</u>	<u>0</u>
TOTALS	M	15	29	0
	F	<u>26</u>	<u>48</u>	<u>2</u>
BOTH		41	77	2
				(-----)

% Affected
Offspring 2.6
S. E. 1.84

S.E. = standard error

(S.E. = r/\sqrt{n} ; r = rate,

n = number on which the rate is based)

CHD = congenital heart defect

PDA = patent ductus arteriosus

VSD = ventricular septal defect

VSD = ventricular septal defect
 PDA = patent ductus arteriosus
 CHD = congenital heart defect

(S.E. = r / (n - 1))
 S.E. = standard error
 n = number on which the rate is based

S.E. = standard error
 n = number on which the rate is based

Diagnosis of Patient	Sex	% with Offending	% Offending	% Offending
TOTALS	M	32	32	32
	F	30	30	30
Ventricular Septal Defect	M	12	12	12
	F	10	10	10
Transposition	M	0	0	0
	F	0	0	0
Tetralogy of Fallot	M	1	1	1
	F	1	1	1
Pulmonic Stenosis	M	1	1	1
	F	2	2	2
Patent Ductus Arteriosus	M	1	1	1
	F	16	16	16
Coarctation	M	3	3	3
	F	2	2	2
Atrial Septal Defect	M	1	1	1
	F	12	12	12
Bicuspid Aortic Valve	M	3	3	3
	F	0	0	0

DISCUSSION

Congenital Heart Defects in Siblings

The prevalence of congenital heart defects in the siblings of the patients in this investigation agreed with that reported in the literature. The published rates vary from 14.2 affected siblings per 1000 live sibling births (Polani and Campbell, 1955) to 18 per thousand (McKeown, MacMahon and Parsons, 1953). It was felt that the data in the present study from the patients and affected siblings with proven or probable diagnoses (Tables 10 and 13) were the most comparable with those reported by others. The prevalence of affected siblings in this group was 12.8 per 1000. While this rate was slightly lower than the figure reported by Polani and Campbell (1955), it was not significantly different.

The prevalence of affected siblings was not constant in all diagnostic categories, as is seen in Table 10. The highest rates of congenital heart defects were found in the siblings of patients with transposition of the great vessels (30.3/1000) and coarctation of the aorta (23.5/1000); the lowest figure appeared in the siblings of patients with atrial septal defects (3.8/1000). However, the numbers of patients and siblings were small when the patients were divided into their diagnostic categories, and there was no statistical variation of the results.

The frequency of the affected siblings of patients in each diagnostic group is presented graphically in Figure 2.

DISCUSSION

Congenital Heart Defects in Siblings

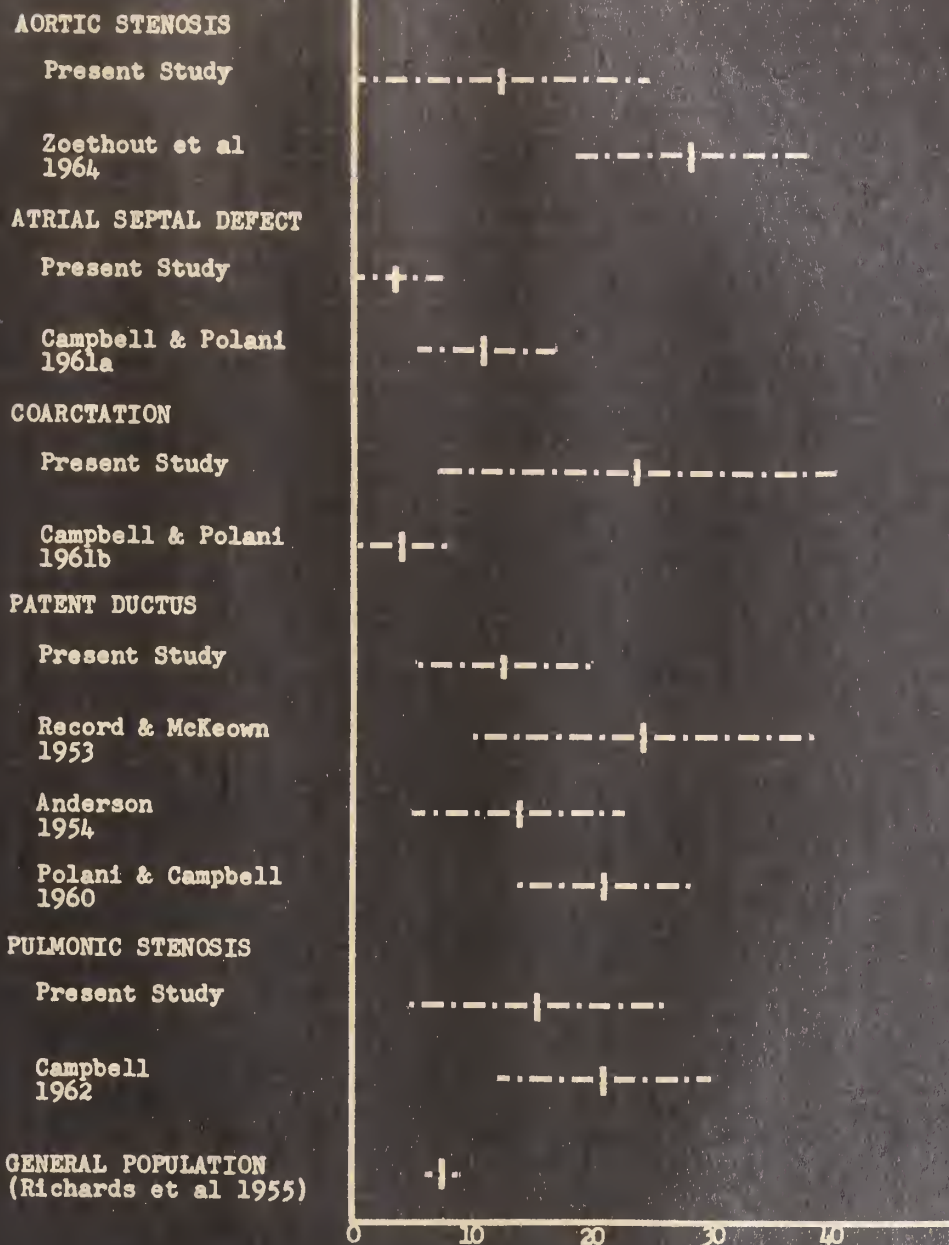
The prevalence of congenital heart defects in the siblings of the patients in this investigation agreed with those reported in the literature. The published rates vary from 11.2 affected siblings per 1000 live sibling births (Poland and Campbell, 1955) to 18 per thousand (McKusick, MacMahon and Pearson, 1955). It was felt that the data in the present study from the patients and affected siblings who proved to have probable diagnoses (Tables 10 and 13) were the most comparable with those reported by others. The prevalence of affected siblings in this group was 15.8 per 1000. While this rate was slightly lower than the figure reported by Poland and Campbell (1955), it was not significantly different. The prevalence of affected siblings was not constant in all diagnostic categories, as is seen in Table 10. The highest rates of congenital heart defects were found in the groups of patients with transposition of the great vessels (30.7/1000) and coarctation of the aorta (23.5/1000); the lowest figure appeared in the siblings of patients with septal defects (3.8/1000). However, the number of patients and siblings were small when the patients were divided into their diagnostic categories, and there was no statistical variation of the results.

The frequency of the affected siblings of patients in each diagnostic group is presented graphically in Figure 1.

Figure 2

- 76 -

CHD IN SIBLINGS OF PATIENTS IN SPECIFIC DIAGNOSTIC CATEGORIES

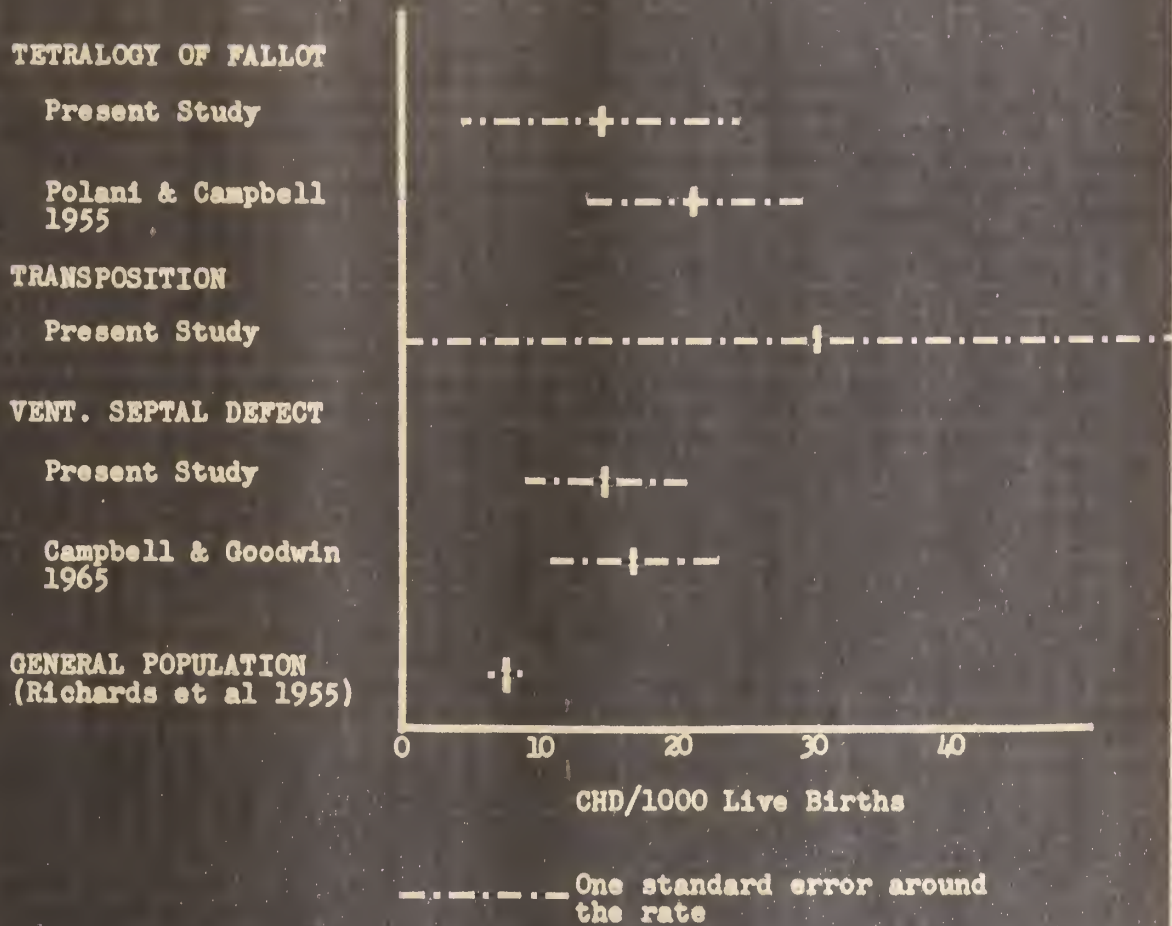


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next page

CHD/1000 Live Births

----- One standard error around
the rate

Figure 2 - continued



Rates from the studies reported in the literature were included for comparison. There is no reported study of the family history of persons with transposition of the great vessels. Discrepancy between the results from this study and the data of others was noticeable only in the atrial septal defect and coarctation of the aorta groups. Again, however, the numbers were small (Tables 5 and 10), and the differences not significant.

In all diagnostic categories, a rate of affected siblings has been reported which is higher than the accepted incidence of congenital heart defects in the general population as found by Richards, Merritt, Samuels and Langmann (1955). Their figure of 7.64 affected persons per 1000 live births including neonatal deaths is the highest published rate of cardiovascular malformations in a general population.

The consistent finding in the literature and the present survey that cardiac anomalies appear more frequently than expected in the siblings of patients is an important observation that must be taken into account when formulating a theory for the etiology of congenital heart defects. Because the present investigation was carried out under different circumstances from the study of Richards and associates, it is not possible to make a precise comparison between the results. Nevertheless, the magnitude of the increased rate of cardiac malformations in the siblings of patients as compared to the expected prevalence is suggested by a statistical comparison between the data of the two studies. There is a significant dif-

ference ($p = < .05$) when all patients and siblings are tabulated as in Table 9. When only patients and affected siblings with proven or probable diagnoses are included (Table 10), there is no statistical significance ($p = 0.07$). This comparison is considered to be the more meaningful, since Richards and associates felt sure of the diagnosis in all affected infants, although it was not proven in every case.

No definitive study has yet been published in which the rate of affected siblings of patients with cardiac anomalies was directly compared with a control population, although the report by Lamy, deGrouchy and Schweisguth (1957) came closest to the ideal. For such a study the patients should all have well established diagnoses, and they should be carefully matched to a control group. Variables in the siblings such as the frequency of prenatal disturbances, maternal age at the time of birth, sex, race, social class and the number of siblings would have to be held constant. Both groups should be investigated under uniform conditions, and preferably the persons investigating the family history should be unaware of which patients had the cardiac lesion.

The study carried out by Lamy and associates had two weaknesses. Their control group was not entirely free of bias, as the consanguinity rate was higher in their patients than in the controls, and they do not specify which factors they held constant in selecting their controls. Secondly, the cardiac defect was not well defined in about one-third of their patients. Nevertheless, their study is the most complete to date,

Table 9, when only patients and controls are compared (p = 0.05) when all patients and controls are compared as in Table 9. When only patients and controls are compared (p = 0.05), there is no statistical significance (p = 0.05). This comparison is considered to be the more significant, since patients and controls are compared in this comparison. All affected individuals, although it was not proven in every case. No statistically significant difference was observed in the rate of affected siblings of patients with similar anomalies was directly compared with a control population, although it was not proven in every case (p = 0.05) (Table 10). In such a study the patients should be well established diagnosis, and they should be carefully selected to a control group. Patients should be affected by the same or general phenomenon, patients should be of the same sex, race, social class and the number of children should be the same. All groups should be investigated by the same method, and preferably by the same investigator. The family history should be reviewed which relates to the same condition. The study carried out by Levy and his colleagues was designed. Their control group was not directly affected by the same congenital anomaly as the patients. They were not directly affected by the same congenital anomaly, and they are not directly affected by the same congenital anomaly. Secondly, the patients and controls were not well defined in their investigation. Therefore, their results are not valid.

and it seemed worthwhile to compare in detail the results of the present study with those reported by them from Paris.

Lamy and co-workers divided their patients into diagnostic classifications somewhat differently than was done for the current investigation. They defined their groups as follows:

Group

- I Fallot's tetralogy and pentalogy.
- II Pulmonary valvular stenosis either as a unique defect or accompanied by atrial septal defect.
- III Patent ductus arteriosus with or without another heart defect.
- IV Ventricular septal defect.
- V Atrial septal defect
- VI Coarctation of the aorta
- VII Precise diagnosis has either not been possible or the defect was extremely complex.
- VIII Well defined but uncommon anatomical defects. Among these are:
 - 1. Abnormal coronary arteries
 - 2. Atrioventricular communis
 - 3. Transposition of the great vessels
 - 4. Eisenmenger's complex
 - 5. Moderate truncular pulmonary atresia
 - 6. Valvular aortic stenosis
 - 7. Tricuspid atresia
 - 8. Dextrocardia
 - 9. Situs inversus with or without congenital heart disease

Insofar as possible, the patients in the present study were rearranged into the above categories. The results of the reclassification are presented in Table 17, along with the breakdown of the patients of Lamy and associates. The

and is aimed primarily to compare in detail the results of the present study with those reported by other workers. They and co-workers divided their patients into three basic classifications somewhat differently than was done for the current investigation. They defined their groups as follows:

Group

- I Fallot's tetralogy and pentalogy
- II Infundibular stenosis either as a unit or defect or accompanied by atrial septal defect.
- III Patent ductus arteriosus with or without another heart defect.
- IV Ventricular septal defect.
- V Atrial septal defect
- VI Coarctation of the aorta
- VII Stenosis diagnosis has either not been possible or the defect was extremely complex.
- VIII Well defined but uncommon anatomical defects. Among these are:
 1. Abnormal coronary arteries
 2. Atrioventricular anomalies
 3. Transposition of the great vessels
 4. Eisenmenger's complex
 5. Moderate tricuspid, pulmonary or aortic stenosis
 6. Valvular aortic stenosis
 7. Tricuspid atresia
 8. Dextrocardia
 9. Situs inversus with or without congenital heart disease

Except as possible, the patients in the present study were rearranged into the above categories. The results of the classification are presented in Table IV, along with the breakdown of the patients of each group and associated.

Table 17

THE PREVALENCE OF CHD IN SIBLINGS: A COMPARISON WITH THE DATA FROM THE PRESENT STUDY WITH THAT OF LAMY ET AL (1957)

Present Study

-----Diagnosis-----									
	I T/F	II PS	III PDA	IV VSD	V ASD	VI COARC	VII ?	VIII MISC	TOTAL
# Patients	63	58	97	172	89	30	89	119	717
% of Total	8.8	8.1	13.5	24.0	12.4	4.2	12.4	16.6	100
# Siblings	142	119	242	353	232	71	220	246	1625
# # with CHD	2	2	3	5	1	2	5	1	21
% with CHD	1.41	1.68	1.24	1.42	0.43	2.81	2.27	0.4	1.29
S. E.	1.0	1.19	0.72	0.64	0.43	1.99	1.01	0.4	0.28

Lamy et al (1957)

	I T/F	II PS	III PDA	IV VSD	V ASD	VI COARC	VII ?	VIII MISC	TOTAL
# Patients	238	56	136	143	97	54	332	132	1188
% of Total	20.0	4.7	11.5	12.0	8.2	4.6	27.9	11.1	100
# Siblings	404	107	249	213	161	78	594	239	2045
# with CHD	4	4	3	1	2	2	13	1	30
% with CHD	1.00	3.74	1.20	0.47	1.24	2.56	2.19	0.42	1.46
S. E.	0.5	1.87	0.69	0.47	0.88	1.81	0.61	0.42	0.27

Table 17 - continued

Key:

T/F = tetralogy of Fallot
PS = pulmonic stenosis
PDA = patent ductus arteriosus
VSD = ventricular septal defect
ASD = atrial septal defect
COARC = coarctation of the aorta
? = diagnosis not certain, or very complicated
MISC = miscellaneous

S.E. = standard error = r/\sqrt{n}

r = rate

n = number on which rate is derived.

Note:

% siblings with CHD x 10 = affected siblings/1000 live
sibling births.

Table IV - continued

Key:

T/P - tetralogy of Fallot
 PS - pulmonary stenosis
 PDA - patent ductus arteriosus
 VSD - ventricular septal defect
 ASD - atrial septal defect
 COA - coarctation of the aorta
 ? - diagnosis not certain, or very complicated
 MISG - miscellaneous

S.E. = standard error = $\sqrt{\frac{r}{n}}$

r = rate
 n = number on which rate is based.

Note:

* siblings with GHD & IG = affected siblings/1000 live
 sibling births.

major differences between the distribution of patients was found in the tetralogy of Fallot, ventricular septal defect, uncertain, and miscellaneous groups; Lamy and co-workers had an excess of patients with the tetralogy of Fallot, and with uncertain diagnoses, while the present group was weighted by patients with ventricular septal defects and aortic stenosis (included as miscellaneous by Lamy and co-workers). The eight-year difference between the time of data collection is probably responsible for the increased numbers of aortic stenosis cases in the present series, because of the increased awareness of this disorder in recent years.

In spite of these differences, however, the rate of affected siblings is quite similar between the two studies. The only noticeable variations are in diagnostic groups II, IV, and V (pulmonary valve stenosis, ventricular septal defect, and atrial septal defect). However, all of these rates are based on small numbers, and there is no significant difference between the results of the two studies.

The presence of an increased number of persons with a congenital heart defect in the siblings of patients with such malformations does not in itself prove that genetic factors are responsible for cardiac anomalies. Many investigators, including McKusick (1964b), have wondered whether the apparent increase is caused by a few instances in which there is definite simple inheritance involving many members in a family; perhaps the patient populations are weighted by these exceptional cases, which raise the over-all figure to a near-

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significant level, even though the majority of affected siblings are afflicted by chance. It is seen in Tables 1 and 2 that there have been reports of families in which as many as six siblings have evidence of a cardiac anomaly. However, this situation is the exception, and in only two families of the present study were more than two members of any family afflicted (cases R.M. and J.C.); in both of these cases heart malformations were believed present in the patient, one sibling and a parent. Thus, there is no weighting of the data from a single family. In the study by Lamy and associates, there were no patients with more than one affected relative.

Siblings are generally exposed to similar environments, including prenatal conditions. It is, therefore, possible that the observed clustering of cardiac defects within families is caused by environmental factors. All that can be said at the present time is that there appears to be an increased frequency of cardiac malformations in the siblings of patients with congenital heart defects. More will be said about the possible inheritance of such lesions in the discussion of the specific defects.

Twins

There were no affected twin siblings of the 20 patients in the study who had a twin. It is not known with certainty that any of these twins were identical, but 11 were definitely non-identical.

The presence of a cardiac defect in only one twin of proven monozygotic origin is not an unusual finding (Table 3).

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The presence of a cardiac defect in only one twin of a monozygotic pair is not an unusual finding (Table 3).

This fact is perhaps the strongest argument against the hypotheses that cardiac malformations are inherited. It can be argued that cardiac anomalies are caused by an interaction of genetic and environmental factors and that although the same genes are present in monozygotic twins, the intra-uterine environments of each twin may be different enough to cause the expression of the defect in one and not the other. An unequal distribution of blood to the two fetuses is one possible variation of prenatal environment that could be of significance.

A second and remote explanation for discordance in identical twins that is consistent with a genetic etiology for congenital heart defects is that an undetectable chromosomal aberration has occurred in these twins at the time of cleavage; the deletion in one twin, or the excess material in the other might be responsible for the anomaly. Small alterations of chromosomes cannot be observed with the present methods of study.

Congenital Heart Defects in Parents

The prevalence of congenital heart deformities in an adult population is not known. Thus it is impossible to evaluate the finding of five affected parents of 717 patients (1434 parents). The rate of congenital heart defects in the general population used earlier (Richards, Merritt, Samuels and Langmann, 1957) is not valid for adults since it includes many infants who have died with their defects.

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The prevalence of congenital heart anomalies in the 1434 parents of the patients in this study was 3.5 affected parents per thousand. Previous studies have reported a varying rate (Table 5). In almost all patient populations, including groups of patients with heterogeneous types of congenital heart defects as well as groups of patients with specific lesions, there were either no affected parents, or only one or two. The only exception was the report by Campbell and Polani (1961a); in a series of 170 patients with atrial septal defects, there were four parents with the same anomaly, a prevalence of 11.7 affected parents per 1000 in a population at risk of 340 people.

Congenital Heart Defects in Offspring

The incidence of cardiac malformations in the offspring of patients in this study was very high (26/1000 live births), although the significance of this rate is diminished because of the small numbers on which it is based (two infants out of 77; Table 16). However, if the rate is accurate, it is considerably higher than the incidence of heart anomalies in the general population reported by Richards, Merritt, Samuels and Langmann (1955) of 7.64 affected persons per 1000 live births.

The only major investigation of the offspring of patients with congenital heart defects was that of Neill and Swanson (1961). They found 18 cases of cardiac anomalies per 1000 live offspring births. Patients with conotruncus abnormalities had the highest percentage of congenitally deformed

The prevalence of congenital heart anomalies in the 1958 survey of the patients in this study was 1.5 affected persons per thousand. Previous studies have reported a varying rate (Table 7). In almost all patient populations, including groups of patients with heterogeneous types of congenital heart defects as well as groups of patients with specific lesions, there were either no affected persons, or only one or two. The only exception was the report by Campbell and Wilson (1961a); in a series of 170 patients with atrial septal defects, there were four persons with the same anomaly, a prevalence of 11.7 affected persons per 1000 in a population at risk of 340 people.

Congenital Heart Defects in Offspring

The incidence of cardiac malformations in the offspring of patients in this study was very high (2/1000 live births), although the significance of this rate is diminished because of the small numbers on which it is based (two infants out of 77; Table 16). However, if the rate is accurate, it is considerably higher than the incidence of heart anomalies in the general population reported by Richardson, Smith, Campbell and Langman (1952) of 4.0 affected persons per 1000 live births. The only major investigation of the offspring of patients with congenital heart defects was that of Hall and Swanson (1961). They found 14 cases of cardiac anomalies per 1000 live offspring. Patients with congenital anomalies had the highest percentage of congenitally defective

children, although it should be noted that their institution had an exceptionally high proportion of patients with conotruncus anomalies.

Whether or not the apparent increase of affected offspring is caused by genetic factors is not certain; a much more detailed investigation is necessary. Perhaps the high rate is at least partially caused by hypoxia in cyanotic mothers. The advancement of cardiac surgery during the last 20 years has permitted many children to reach maturity who formerly would have died. The first generation of such patients is just now reaching the age of reproduction, and in another few years the number of offspring born to congenital heart defects patients will undoubtedly rise substantially. A careful study of these offspring seems warranted. Since there is no evidence to date that cardiac anomalies are sex linked characteristics, perhaps the most meaningful investigation of genetic factors would be a study of the offspring of male patients, so that the possibility of altered physiology from the heart defect would not influence the prenatal environment of the fetus.

Duplication of Specific Cardiac Defects

Congenital heart defects comprise a wide spectrum of disorders, and it is reasonable to assume that there could be different etiologic factors for the various categories. It has already been seen that the frequency of affected siblings

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Classification of Specific Cardiac Defects

Congenital heart defects comprise a wide spectrum of disorders, and it is reasonable to assume that there could be different etiologic factors for the various categories. It has already been seen that the frequency of affected siblings

was probably elevated in patients in each diagnostic group. The next question is whether or not siblings and other close relatives tend to be afflicted with the same or different lesions. Intuitively, one would expect the same defect in each family member if there is a common, specific etiologic agent, such as a single gene, which causes the cardiac anomaly. However, it is also possible that a particular etiologic factor may predispose to the development of cardiac malformations in general.

Duplication of a lesion within a family has been said to occur more frequently than discordant heart defects (Nadas, 1963; McKusick, 1964b), although this has not been a universal experience (Lamy, deGrouchy and Schweisguth, 1957). In the present study, it was found that in 17 of the 29 families with multiple afflicted persons, the same lesion was present in all affected members, although in eight families there was an additional cardiac problem. In another eight families the malformations were entirely different, so far as could be determined, and in four cases the exact nature of the heart defect in the affected relative was not known (Tables 14, 15, and 16). Thus, identical or partially identical anomalies were present in 59% of the families in which two or more persons had a congenital cardiac anomaly.

Of particular note is the finding that in all but one case in which a parent and child were affected, the lesions were the same in both, although in several instances there were additional defects in one person (Tables 15 and 16). The one exception was in the offspring of a patient noted in Table 16;

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the patient was thought to have an atrial septal defect, and her child a ventricular septal defect. However, the patient had not been seen for many years, and it is possible that she had a defect in her ventricular septum. It, therefore, appears that the same lesion tends to be duplicated when the malformations appear in successive generations. In the only study of the offspring of patients (Neill and Swanson, 1961), no comment was made about the similarity or dissimilarity of cardiac malformations. However, in the reports in the literature of heart defects appearing in more than one generation of a family (Table 1), identical lesions were the rule with few exceptions.

At least one example of a duplicated anomaly was seen in patients from the present study in every diagnostic category, and there have been reports of the repetition of all these malformations in the literature. One diagnostic group, however, is worthy of special comment, namely aortic stenosis.

It is now recognized that aortic stenosis can be divided into four separate types: valvular, supra- and subvalvular and idiopathic hypertrophic subaortic stenosis (Nadas, 1963). Valvular aortic stenosis is the most common form. Supra- and subvalvular stenosis consists of a fibrous obstruction distal to the aortic valve, and in subvalvular stenosis there is a discrete fibrous ring encircling the left ventricular outflow tract a few millimeters below the aortic valve. The most recently described form of aortic stenosis is idiopathic hypertrophic subaortic stenosis, otherwise known as concentric

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hypertrophy of the left ventricle, muscular subaortic stenosis or idiopathic congenital left ventricular hypertrophy, and about which more will be said later. It was not possible to place all the patients with aortic stenosis in the present study into the specific categories, since many of these patients were evaluated prior to the recognition of the various forms of the disorder, and insufficient data was recorded. However, it is felt that all patients probably had either the valvular or subvalvular type.

The familial nature of idiopathic hypertrophic subaortic stenosis has been described on numerous occasions (Braunwald, Lambrew, Rockoff, Ross and Morrow, 1964; Brent, Akio, Fisher, Moran, Myers and Taylor, 1960). Braunwald and associates (1964) recently reviewed the genetics of the disease and found that there was consistent evidence for a dominant inheritance, but that in some series of patients the defects appeared to be sex-linked, while in others the findings were consistent with an autosomal dominant inheritance. As many as 30 related persons have been thought to have idiopathic hypertrophic subaortic stenosis, although in most pedigrees many persons were diagnosed only by the history of sudden death or an ill-defined heart problem (Pare, Fraser, Pirozynski, Shanks, and Stubington, 1961).

Two patients in the present study were thought to have a close relative with idiopathic hypertrophic subaortic stenosis. They are M.L. and J.M. (Tables 15 and 16). M.L. had a clinical diagnosis of ventricular septal defect made many years ago, and she has been lost to follow-up. Her brother died in this hospital while undergoing surgery for suspected mitral stenosis.

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At post mortem examination, the right and left ventricle were found to be tremendously hypertrophied, and there was a protrusion of the intraventricular septum into the left ventricle; this bulge apparently functioned as an obstruction to the left ventricular outflow tract. Similar findings have been reported by Braunwald, Lambrew, Rockoff, Ross and Morrow (1964).

The second with a relative thought to have idiopathic hypertrophic subaortic stenosis had a diagnosis of aortic valvular stenosis based upon catheterization data. However, the catheterization procedure was not completely satisfactory because of the anxiety of the patient, and it is possible that the obstruction was not entirely valvular. His father died suddenly at the age of 38 years. At autopsy, the left ventricle was tremendously hypertrophied, and the microscopic findings were consistent with those described by Braunwald and co-workers (1964).

If, indeed, these relatives had idiopathic hypertrophic subaortic stenosis, and if the heart lesions are inherited in the two families, it is surprising that the patients had different diagnoses.

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If, indeed, these relatives had idiopathic hypertrophic subaortic stenosis, and if the heart lesions are inherited in the two families, it is surprising that the patients had different diagnoses.

SUMMARY AND CONCLUSIONS

The prevalence of congenital heart defects in the siblings, parents and offspring was determined in a series of 717 patients with congenital cardiac anomalies. These patients were drawn by random sampling technique from patients with heart malformations registered in a demonstration pediatric cardiac clinic between 1947 and 1960. Family history information was updated by questionnaires sent to the 82% of patients for whom current addresses were available; 78% of the questionnaires were returned, representing 64% of total patient population. Further information on near relatives with suspected heart lesions was obtained from physician and hospital records and by personal examination. The specific cardiac diagnosis was proven in 59% of the patients and in 52% of affected relatives. The prevalence of affected siblings was 12.8 per 1000 live sibling births in cases where the diagnosis of the specific heart defects was proven or reasonably certain in both patient and sibling. If possibly affected patients and siblings were included, the rate was 14.8 per 1000. This figure is approximately twice the incidence of congenital heart malformations in the general population of 7.64 per 1000 live births as found by Richards and associates (1955).

The rate of affected parents was lower than that of siblings and was 3.5 per 1000 parents.

A high incidence of heart anomalies (23.5/1000 live births) was found in the offspring of the patients, although

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A high incidence of heart anomalies (23.5/1000 live
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the numbers of known offspring was small (77).

Similar defects were found in the patients and their affected relatives in 59% of the 29 families in which there were more than two persons with heart malformations. In the seven families where affected individuals were in sequential generations, the lesions were similar in six cases.

It, therefore, appears that congenital cardiac defects are inherited in some families, although the precise role of genetics in this disorder is still unclear.

the number of known offspring was small (7%).

Similar defects were found in the patients and their affected relatives in 9% of the 29 families in which there were more than two persons with heart malformations. In the seven families where affected individuals were in sequential generations, the lesions were similar in all cases.

It, therefore, appears that congenital cardiac defects are inherited in some families, although the precise mode of genetics in this disorder is still unclear.

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CHD-II
II-1

NHRF MEDICAL CODE FOR HEART DISEASE (MODIFIED)

-- CLINICAL INFORMATION

IDENTIFYING DATA

Items thus marked should be recorded in the space provided on the Additional Medical Information Sheet (such as deaths, combination of defects, relationships not otherwise specified, numbers and types of abnormal pregnancies, etc.)

For example: In Col. 22, number 8, specify the relationship to patient of individuals involved - such as - mother had rheumatic fever and sibling had congenital heart defect.

Col. 1 IBM CARD
(Type and number in present series)

- 0
- 1 Identification
- 2 CHD 1
- 3 CHD 2
- 4 RF, RHD 1
- 5 Laboratory
- 6 Electrocardiogram
- 7
- 8
- 9

Col. 2-3 SUBSAMPLE NUMBER

Example - 1 = 01
2 = 02
10 = 10

Col. 4-7 NHRF NUMBER

Example - under 1000 = 0111

(Col. 2-7 will be space for G-NHCH Chart Number)

Col. 8-9 YEAR OF BIRTH

Col. 12-13 MONTH DATA OBTAINED
FROM PATIENT (most recent)

Col. 10-11 MONTH OF BIRTH

Col. 14-15 YEAR DATA OBTAINED
FROM PATIENT (most recent)

Col. 16-17 AGE IN YEARS
DATA OBTAINED
(when last seen)

Col. 18-19 AGE IN MONTHS
DATA OBTAINED
(when last seen)

Col. 20 MULTIPLE PREGNANCY

- 0 Single pregnancy
- 1 Twin identical male
- 2 Twin identical female
- 3 Twin unidentical male
- 4 Twin unidentical female
- 5 Twin unidentical male and female
- 6 Twin unknown
- 7 Other multiple pregnancies
- 8
- 9 Unknown

Col. 21 F.H. ALLERGY (Asthma, hay fever, hives, rash to foods) Allergy to drugs not to be included here but on abstraction sheet.

- 0 None
- 1 Parent - one
- 2 Both parents
- 3 Siblings
- 4 Parents (one or both) and sibling
- 5 Other relatives
- 6 Parents & relatives
- 7 Sibling & relatives
- 8 Parent, sibling & relatives
- 9 Unknown

FAMILY HISTORY

("Near relatives" include grandparents, aunts, uncles, nephews, nieces and first cousins)

Col. 22-23 FAMILY HISTORY OF RHEUMATIC FEVER, RHEUMATIC HEART DISEASE OR CONGENITAL HEART DISEASE (Living or Dead)

Col. 22 PARENTS AND SIBLINGS

- 0 None
- 1 CHD in sibling
- 2 CHD in parent
- 3 CHD in sibling & parent
- 4 RF in sibling
- 5 RF or RHD in parent
- 6 RH or RHD in both parent and sibling
- 7 Murmur of unknown etiology in sibling
- *8 Combined RF & CHD
- *9 Unknown (or record combination not otherwise indicated)

Col. 23 OTHER NEAR AND DISTANT RELATIVES

- 0 None
- 1 CHD in near relative except parent or sibling
- 2 CHD in distant relative only
- 3 CHD in near relative (who is not parent or sibling) plus distant relatives
- *4 RF in near relative
- *5 RF in distant relative
- *6 RF in near & distant relative
- *7 RF in 2 or more near & distant relatives
- *8 Combined RF & CHD
- *9 Unknown, or record combination not otherwise indicated

Col. 24-25 FAMILY HISTORY OF NON-CARDIAC CONGENITAL MALFORMATIONS (*Specify type)

Col. 24 PARENTS AND SIBLINGS

- 0 None
- 1 Sibling
- 2 Parent
- 3 Sibling and parent
- *4 Death (or illness) of sibling etiology unknown
- *5 Death of sibling due to non-cardiac congenital abnormality
- 6
- 7
- *8 Combination
- *9 Unknown

Col. 25 OTHER NEAR AND DISTANT RELATIVES

- 0 None
- *1 Near relatives except parents and siblings
- *2 Distant relatives only
- *3 Near relatives who are not parents or siblings plus distant relatives
- 4
- 5
- 6
- 7
- 8
- *9 Unknown (record deaths)

FAMILY HISTORY (CONT.)

Col. 26-27 FAMILY HISTORY OF DIABETES

Col. 26 PARENTS

- 0 None
- 1 Diabetic mother
- 2 Diabetic father
- 3 Both parents diabetic
- 4 Prediabetic mother with diabetic father
- 5 Prediabetic mother without diabetic father
- 6
- 7
- 8
- 9 Unknown

Col. 27 OTHER RELATIVES

- 0 None
- Siblings
- 1 Siblings
- 2 Siblings plus near relatives
- 3 Siblings plus distant relatives
- 4 Siblings plus near and distant relatives
- No siblings
- 5 Near relatives only
- 6 Near and distant relatives
- 7 Distant relatives only
- 8
- 9 Unknown

COL. 28 OMITPREGNANCY HISTORY

If prenatal history is partially recorded in NHRF,
assume all questions asked.

Use "Unknown" if no prenatal history recorded
as in foster or adopted child.

Col. 29 TOTAL NUMBER OF
MATERNAL PREGNANCIES

- (Including patient & current pregnancy if present)
- 0 (Not applicable -- i.e., foster or adopted child)
- 1 1
- 2 2
- 3 3
- 4 4
- 5 5
- 6 6
- 7 7
- *8 8 or more*
- 9 Unknown

Col. 30 TOTAL NUMBER OF AB-
NORMAL PREGNANCIES

- (Miscarriage, abortion, stillbirth, etc. Do not include congenital malformations including congenital heart disease.)
- 0 No abnormal pregnancies
- 1 1
- 2 2
- 3 3
- 4 4
- 5 5
- 6 6
- 7 7
- *8 8 or more*
- 9 Unknown

If Col. 30 = 9, Col. 29 = total number of live births only
(i.e., number of abnormal pregnancies unknown)

PREGNANCY HISTORY (CONT.)

Col. 31 MATERNAL BLEEDING

(Menstrual, spotting, etc.
except for "scant period"
at end of first month)

- 0 None
- 1 1st trimester
- 2 2nd trimester
- 3 3rd trimester
- 4 First 2 trimesters
- 5 Last 2 trimesters
- 6 All 3 trimesters
- 7 Bleeding - unspecified
as to when (time)
- 8
- 9 Unknown

COL. 33 OMITCol. 32 EXCESSIVE MORNING
SICKNESS (Vomiting)

- 0 No excessive morning sick-
ness
- 1 Excessive morning sickness
present
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9 Unknown

Col. 34 TOXEMIA

- 0 No toxemia
- 1 Toxemia present
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9 Unknown

Col. 35 ANTENATAL GERMAN
MEASLES (Rubella)

- 0 No German measles
- 1 German measles 1st tri-
mester
- 2 German measles 2nd tri-
mester
- 3 German measles 3rd tri-
mester
- 4
- 5
- 6
- 7
- 8
- 9 Unknown

Col. 36 EXPOSURE TO GERMAN
MEASLES OR GERMAN MEASLES
EPIDEMIC BUT NO KNOWN
ILLNESS

- 0 None
- 1 1st trimester
- 2 2nd trimester
- 3 3rd trimester
- 4 First 2 trimesters
- 5 Last 2 trimesters
- 6 All 3 trimesters
- 7 Not applicable
- 8
- 9 Unknown

*Col. 37 "VIRUS" INFECTIONS
OTHER THAN GERMAN MEASLES
(Specify which, if possible,
bacterial infections)

- 0 None
- 1 1st trimester
- 2 2nd trimester
- 3 3rd trimester
- 4 First 2 trimesters
- 5 Exposure only to virus in-
fection(s) (not contracted)
(other than German measles)
or virus epidemic:
SPECIFY WHICH
- 6 Combinations
- *7 Other bacterial infections
(when)
- 8
- 9 Unknown

PAST HISTORYCol. 38 PARENTS' AGE AT
BIRTH OF PATIENT

- 0 Both under 20
- 1 Either one under 20 -
other not over 40
- 2 Both between 20 and 40
- 3 One parent under 40,
other = ?
- 4 Mother over 40, father
between 20-40
- 5 Mother over 40, father = ?
(or under 20)
- 6 Father over 40, mother
between 20-40
- 7 Father over 40, mother = ?
(or under 20)
- 8 Both over 40
- 9 Unknown

COL. 40-42 OMIT

Col. 39 BIRTH WEIGHT

- 0
- 1 Under 2 lbs.
- 2 2-3 lbs. 15+ ozs.
- 3 4-5 lbs. 8 oz.
- 4 5 lbs. 9 ozs. -
7 lbs. 15+ ozs.
- 5 8-10 lbs. 15+ ozs.
- 6 11-14 lbs. 15+ ozs.
- 7 15 lbs. or over
- 8
- 9 Unknown

Col. 43 ALLERGY

- 0 None
- 1
- 2
- 3
- 4
- 5 Allergy in patient
- 6
- 7
- 8
- 9 Unknown

COL. 44 - OMITPRESENT ILLNESS

Col. 45 FIRST SIGN OR SYMPTOM OF CARDIAC PROBLEM

- 0
- 1 Murmur
- 2 Failure to thrive
- 3 Cyanosis
- *4 Other
- 5 Arthritis
- 6 Fever
- 7 Chorea
- *8 Combination
- 9 Unknown

PRESENT ILLNESS (CONT.)

Col. 46 AGE WHEN DISCOVERED
(IN YEARS)

- 0 Under 1 year
- 1 1 year
- 2 2 years
- 3 3 years
- 4 4 years
- 5 5 years
- 6 6 through 9 years
- 7 10 through 14 years
- 8 15 years or over
- 9 Unknown

Col. 47 AGE IN MONTHS WHEN DIS-
COVERED, IF UNDER ONE YEAR

- 0 Birth (first 5 days)
- 1 Under 3 months
- 2 Under 6 months (ie., 3 months or over but under 6 months)
- 3 Under 9 months
- 4 Under 1 year
- 5 Not applicable
- 6
- 7
- 8
- 9 Unknown

COL. 48-57 OMITPHYSICAL EXAMINATIONCol. 58 HEIGHT
Percentile (Stuart's chart)

- 0
- 1 97th or above
- 2 90th or above
- 3 75th or above
- 4 50th or above
- 5 25th or above
- 6 10th or above
- 7 3rd or above (below 10th percentile)
- 8 Under 3rd
- 9 Unknown

Col. 59 WEIGHT
Percentile (Stuart's chart)

- 0
- 1 97th or above
- 2 90th or above
- 3 75th or above
- 4 50th or above
- 5 25th or above
- 6 10th or above
- 7 3rd or above (below 10th percentile)
- 8 Under 3rd
- 9 Unknown

Col. 60 CYANOSIS

- 0 No cyanosis
- 1 1+ at rest ("?" or "very mild" - "some" - no clubbing)
- 2 2+ at rest (mild)
- 3 3+ at rest (moderate to marked)
- 4 4+ at rest (severe)
- 5 Only on exertion
- *6 Differential
- 7 History but not seen, i.e., on exertion
- 8 History of cyanosis associated with pulmonary disease
- 9 Unknown

COL. 61-63 OMIT

PHYSICAL EXAMINATION (CONT.)

Col. 64 BLOOD PRESSURE -- ARM VS. ARM, AND ARM VS. LEG
(+ or - 10 mm. Hg. systolic)

- 0
- 1 Arm less than leg
- 2 Arm equals leg with normal pressures
- 3 Arm greater than leg with normal pressures
- 4 Arm greater than leg with hypertension in arms
- 5 Hypertension in one arm only with hypertensive arm greater than other arm or legs
- 6 Hypotension in one arm only (greater than 15 mm. Hg. lower than other arm)
- 7 Arm only
- 8
- 9 Unknown or not obtained

Col. 65 BLOOD PRESSURE GENERALIZED

- 0 Blood pressure normal -- (0, 1 or 7 in column 64)
- 1 Abnormal differential blood pressure (2-6 in column 64)
- 2 Generalized hypertension - (see Definition A below)
- 3 Generalized hypotension - (see Definition B below)
- *4 Other
- 5 Diastolic hypertension only (Ex. 120/100)
- 6 Hypertension associated with anxiety (usually evidence of normal blood pressure taken at a later date by M.D. or school nurse)
- 7
- 8
- 9 Unknown

Definition A - Hypertension (systolic pressure in arm)

Birth to 10 yrs. - over 120 mm. Hg.
Over 10 yrs. - over 130 mm. Hg.

Definition B - Hypotension (systolic pressure in arm)

Birth to 5 yrs. - under 80 mm. Hg.
Over 5 yrs. - under 100 mm. Hg.

Col. 66 PULSE PRESSURE

(Taken from last recorded arm blood pressure: (Ex.) Pulse pressure of 120/80 = 120-80 = 40)

- 0 Not applicable -- column 64 checked 4, 5, or 6
- 1 Normal pulse pressure, i.e., 20 - 60 mm. Hg. in ~~all~~ ^{arm} extremities
- 2 Pulse pressure increased
- 3 Pulse pressure decreased
- *4 Other (such as decreased pulse pressure in one extremity only, etc.)
- 5
- 6
- 7
- 8
- 9 Unknown

PHYSICAL EXAMINATION (CONT.)COL. 67-74 OMIT

Col. 75 CYANOSIS POSTOP.
(From subsequent surgery)

- 0 None
- 1 Transient
- 2 1-2+
- 3 3-4+
- 4 Not applicable
- 5
- 6
- 7
- 8
- 9 Unknown

Col. 76 INITIAL DIAGNOSIS

- 0 No cardiac problem
- 1 Innocent (functional) murmur
- 2 CHD
- 3 RF or RHD
- *4 Equivocal
- *5 Miscellaneous (arrhythmias, myocarditis, etc.)
- *6 Combination, i.e., RF or CHD, etc. (not functional murmur + IVSD)
- 7
- 8
- 9 Unknown

COL. 77 OMIT

COL. 78-79 NOT USED

Col. 80 REFERENCE NUMBER - Code 1 for pre-operative data
Code 2 for post-operative data

NHRF MEDICAL CODE FOR HEART DISEASE (MODIFIED)

-- CLINICAL INFORMATION

IDENTIFYING DATA
(Col. 1-9 as on Card II)

Col. 1	IBM CARD (Type and number in present series)	Col. 2-3	SUBSAMPLE NUMBER
0		Col. 4-7	NHRF NUMBER
1	Identification		
2	CHD 1		
3	CHD 2		
4	RF, RHD 1		
5	Laboratory		
6	Electrocardiogram		
7			
8			
9			

Col. 8-9 YEAR OF BIRTH

COL. 10-43 OMIT

Col. 44 DEXTROCARDIA AND SITUS INVERSUS

0	Normal levocardia (assumed if x-ray or fluoroscopy done but not mentioned)
1	Dextrocardia only
2	Dextrocardia and situs inversus
3	Levocardia with situs inversus
4	
5	
6	
7	
8	
9	Unknown

ELECTROCARDIOGRAM

Col. 45	EKG RHYTHM	Col. 46	EKG AXIS
0	Normal sinus rhythm, sinus arrhythmia or sinus tachycardia	0	Normal 0 to 90°
1	Atrial premature systoles	1	RAD + 90 to 180°
2	Nodal (A-V) premature systoles	2	LAD 0 to -90°
3	Supraventricular tachycardia (other than sinus tachycardia)	3	Northwest - indeterminate
4	Idioventricular rhythm	4	
5	Ventricular premature systoles	5	
6	Ventricular tachycardia	6	
7	Other	7	
*8	Unknown	8	
9		9	Unknown

ELECTROCARDIOGRAM (CONT.)

Col. 47 EKG HYPERTROPHY

(can only be ascertained if
precordial leads are present)

- 0 Normal
- 1 LVH
- 2 LVH with strain
- 3 RVH
- 4 RVH with strain
- 5 Combined VH
- 6 CVH with strain
- *7 LVP
- 8 RVP
- 9 Unknown - no precordial leads, or,
*Other (Record)

Col. 48 EKG CONDUCTION

- 0 Normal or unknown
- 1 1st° heart block
- 2 2nd° heart block
- 3 Complete heart block (3°)
- 4 Right incomplete bundle branch block
- 5 Right incomplete bundle branch block
+ 1st° heart block
- 6 Right bundle branch block
- 7 Left bundle branch block
- 8 Intraventricular block (wide QRS)
only
- *9 Other (including combinations,
specify)
or Unknown - when Cols. 45-47 = 9

LABORATORY TESTS

Col. 49 ARTERIAL SATURATION

- 0 Not done
- 1 Normal saturation
- 2 Unsaturated at all times and with oxygen
- 3 Unsaturated with exercise, normal at rest and/or oxygen
- 4 Unsaturated at rest, normal with oxygen
- 5 Normal saturation with oxygen (single exam.)
- 6 Unsaturated - no oxygen given
- *7 Unclassified
- 8 ? whether done
- 9 Done

Col. 50 CARDIAC CATHETERIZATION

- 0 Not done
- 1 Done
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9 Suspected - not known for sure

Col. 51 CARDIAC ANGIOGRAMS

- 0 Not done
- 1 Done
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9 Suspected - not known for sure

DIAGNOSESCol. 52 ASSOCIATED CONGENITAL
ABNORMALITIES (NON-CARDIAC ANOMALY)

- 0 None
- *1 Eyes
- *2 G. I. sys.
- *3 GU, endocrinopathy
- *4 C.N.S. (include mental retardation -
but NOT mongolism alone) (this in
Col. 74 - 2)
- *5 Musculo-skeletal system
- *6 ENT anomalies - cleft palate, hare-
lip, congenital deafness, dental
anomalies
- *7 Skin
- *8 Other or combinations of above
- 9 Unknown

Col. 53 SHUNT AND FUNCTION

- 0 No functional disturbance
- 1 Left-to-right (exclusively or
predominantly)
- 2 Right-to-left (exclusively or
predominantly)
- 3 Obstruction to total flow with-
out any shunt
- 4 Transposition of the great vessel
- *5 Other
- 6
- 7
- 8
- 9 Unknown

Col. 54 STATE OF PRIMARY DIAGNOSIS (Give clinic diagnosis first)

- 0
- 1 Definite (proven clinically) Include cath and/or surgery only if done before
we saw patient.
- 2 Probable
- 3 Possible
- 4 Alternate
- 5 Past diagnosis with complete recovery - Example: myocarditis other than
rheumatic fever with subsequent recovery
- 6
- 7
- 8
- 9

Col. 55-58 PRIMARY DIAGNOSIS CODE NUMBER PER KEITH

Col. 59 STATE OF SECOND DIAGNOSIS (use also for Col. 64 and 69)

- 0
- 1 Definite
- 2 Probable
- 3 Possible
- 4 Alternate
- 5 Past diagnosis with complete recovery
- *+6 Proven by surgery (specify place if done elsewhere)
- +7 Proven by cath and/or angio
- +8 Proven by autopsy
- +9 Proven by subsequent course, residual or recurrence

+ Try to put these proven diagnoses in 4th or 3rd and 4th places if possible

DIAGNOSES (CONT.)

- Col. 60-63 SECOND DIAGNOSIS CODE NUMBER PER KEITH
- Col. 64 STATE OF THIRD DIAGNOSIS -- See Col. 59
- Col. 65-68 THIRD DIAGNOSIS CODE NUMBER PER KEITH
- Col. 69 STATE OF FOURTH DIAGNOSIS -- See Col. 59
- Col. 70-73 FOURTH DIAGNOSIS CODE NUMBER PER KEITH - Proven diagnosis if possible
- Col. 74 ADDITIONAL DIAGNOSES (non-congenital) (include excessive incidence of respiratory infections, etc.)
Allergy to be included only in Card II, Col. 43.
- 0 None
 - *1 ENT and/or speech (omit dental caries)
 - 2 Mongolism only
 - *3 Metabolic disease
 - 4 Resp. (or infectious disease)
 - 5 Emotional or psych. problems (include habit spasm)
 - *6 Others or combinations
 - *7 CNS acquired problems
 - *8 Post-surgical complications
 - 9 Unknown

TREATMENT AND STATUS

- | | |
|--|---------------------|
| Col. 75 ANTI-BACTERIAL PRO-PHYLAXIS (+8 (for dental etc.) <u>assumed</u> if not otherwise specified) | <u>COL. 76 OMIT</u> |
|--|---------------------|
- 0 None
 - 1 Penicillin Q.D. (every day) +8
 - 2 Penicillin B.I.D. (twice a day) +8 (only when specified)
 - 3 Penicillin by injection +8
 - 4 Sulfa +8
 - 5 Tetracyclines +8
 - *6 Other
 - *7 Combinations of above +8
 - 8 For dental or surgical procedures only
 - 9 Unknown

TREATMENT AND STATUS (CONT.)

Col. 77 CARDIAC DRUGS PRESCRIBED

- 0 None
- 1 Digitalis, type not specified
- 2 Digoxin
- 3 Digitoxin
- *4 Other digitalis preparations
- 5 Quinidine
- 6 Combination of digitalis and quinidine
- *7 Other
- 8 Previous dig. - not now
- 9 Unknown

Col. 78 NUMBER OF CARDIAC OPERATIONS

- 0 None
- 1 1
- 2 2
- 3 3
- 4 4
- 5 5
- 6 6
- 7 7
- 8 8
- 9 Surgery recommended, (but not carried out as yet (awaiting operation)

Col. 79 STATUS

- 0
- 1 Living
- 2 Deceased, no autopsy
- 3 Deceased, autopsy done
- 4 Deceased, autopsy unknown
- *5 Deceased at surgery (indicate if no autopsy)
- 6 Deceased after surgical period with autopsy (i.e., month or more postop.)
- 7 Deceased after surgical period without autopsy
- *8 Deceased after surgery in postoperative period (*indicate if no autopsy)
- 9 Unknown

Col. 80 REFERENCE NUMBER - Code 1 for pre-operative data
Code 2 for post-operative data

APPENDIX B: KEITH'S CODE

Keith's Code Numbers for Congenital Heart Defects

03
04
05
08
09
13
23
27
28
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41
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Keith's Code Numbers for Congenital Heart Defects

03
04
05
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KEITH'S CODE

DIAGNOSTIC CLASSIFICATIONS - CARDIAC REGISTRY

01. 00. ABNORMALITIES OF RHYTHM (ARRHYTHMIAS)

01. Heart block (excluding lengthening PR)
02. Paroxysmal tachycardia - supraventricular (atrial)
03. Paroxysmal tachycardia - ventricular
04. Recurrent paroxysmal tachycardia
05. Persistent paroxysmal tachycardia
06. Atrial flutter
07. Fibrillation - auricular
08. Fibrillation - ventricular
09. Premature systoles - auricular
10. Premature systoles - nodal
11. Premature systoles - ventricular
12. Nodal rhythm
13. Wolf-Parkinson-White syndrome

02. 00. ANAEMIA WITH CARDIAC INVOLVEMENT

03. 00. ANEURYSMS

01. Aneurysm into coronary sinus
02. Aneurysm into bicuspid pulmonary valve
03. Aneurysm of sinus of Valsalva - with rupture
04. Aneurysm of sinus of Valsalva - without rupture

04. 00. ANOMALIES OF THE CORONARY ARTERIES

01. Absence of left coronary artery
02. Absence of right coronary artery
03. Accessory coronary artery
04. Aneurysm of right coronary artery - congenital
05. Anomalous origin of both coronary arteries from pulmonary artery
06. Anomalous origin of left coronary artery from pulmonary artery
07. Anomalous origin of right coronary artery from pulmonary artery
08. Operated cases

REF ID: A66040

;

(CONTINUED) LIST OF TRANSLATIONS

05. 00. ANOMALIES OF VENOUS RETURN

(1-20) Anomalies of Systemic Veins (A)

01. Inferior vena cava into azygos
02. Inferior vena cava to left atrium
03. Left inferior vena cava
04. Left superior vena cava to coronary sinus
05. Left superior vena cava to left atrium
06. Levo-atrial cardinal vein
07. Other

10. Anomaly of systemic venous return - undefined

(21-40) Partial Anomalies of Pulmonary Veins (B)

21. Left pulmonary veins into coronary sinus
22. Left pulmonary veins into left subclavian vein
23. Left pulmonary veins into left superior vena cava
24. Right pulmonary veins into azygos
25. Right pulmonary veins into coronary sinus
26. Right pulmonary veins to right atrium
27. Right pulmonary veins into inferior vena cava
28. Right pulmonary veins into right superior vena cava
29. Right pulmonary veins into superior vena cava plus right atrium

30. Partial anomaly of pulmonary venous return - undefined

(41-60) Total Anomalous Pulmonary Vein Drainage (C)

41. Cardiac: into coronary sinus
42. Cardiac: into right atrium
43. Infracardiac: into ductus venosus
44. Infracardiac: into portal vein
45. Mixed
46. Supracardiac: into left superior vena cava
47. Supracardiac: into superior vena cava
48. Operated

50. Total anomaly of pulmonary venous return - undefined

06. 00. AORTIC ATRESIA

Atresia of aortic valve (including minute openings that are functionally atretic)

07. 00. AORTIC DILATATION OR ANEURYSM

08. 00. AORTIC INSUFFICIENCY

- 01. Congenital
- 02. Acquired

09. 00. AORTIC AND SUBAORTIC STENOSIS (CONGENITAL) - Acquired:
see Rheumatic Fever - 55.8

- 01. Aortic stenosis
- 02. Subaortic stenosis
- 03. Aortic or subaortic stenosis - operated
- 04. Aortic stenosis with aortic insufficiency

10. 00. AORTIC VALVE - OTHER ANOMALIES

- 01. Absent pulmonary valve
- 02. Bicuspid aortic valve
- 03. Bicuspid pulmonary valve
- 04. Other

11. 00. ARTERIO-VENOUS FISTULAE (ANEURYSMS)

12. 00. ATHEROSCLEROSIS IN CHILDHOOD

13. 00. ATRIAL SEPTAL DEFECT

- 01. Atrial septal defect with mitral stenosis (Lutembacher syndrome)
- 02. Atrio-ventricularis communis
- 03. Complete absence of atrial septum
- 04. Persistent ostium primum
- 05. Persistent ostium secundum

(operated - over)

13. 00. ATRIAL SEPTAL DEFECT (continued)

- 06. Operated cases - A. S. D. closure (secundum)
- 07. Operated cases - A. V. Communis
- 08. Operated cases - Persistent ostium primum
- 10. Atrial septal defect with pulmonary hypertension
- 11. Persistent ostium primum with pulmonary hypertension
- 12. Atrial septal defect with other non-specified cardiac deformity

14. 00. BACTERIAL ENDOCARDITIS

- 01. E. coli
- 02. Hemolytic streptococcus
- 03. Non-hemolytic streptococcus
- 04. Pneumococcus
- 05. Staphylococcus
- 06. Streptococcus viridans
- 07. Other - subacute, etc.
- 08. Bernheim's syndrome

15. 00. BRAIN ABSCESS

- 01. -08. Organism as above in 14.
- 09. Mixed infection

16. 00. CARDIAC INVOLVEMENT IN THE COLLAGEN DISEASES

- 01. Dermatomyositis
- 02. Disseminated lupus erythematosus
- 03. Periarteritis nodosa
- 04. Scleroderma
- 05. Other

17. 00. CARDIAC INVOLVEMENT IN GARGOYLISM

18. 00. CARDIAC INVOLVEMENT IN HYPO- and HYPERTHYROIDISM

- 01. Hyperthyroidism
- 02. Hypothyroidism

19. 00. CARDIAC INVOLVEMENT IN NEUROMUSCULAR DYSTROPHIES

- 01. Friedrich's ataxia
- 02. Progressive muscular dystrophy

20. 00. CARDIAC INVOLVEMENT IN RHEUMATOID ARTHRITIS

- 01. Rheumatoid arthritis with no cardiac involvement
- 02. Rheumatoid arthritis with pericarditis
- 03. Rheumatoid arthritis with other cardiac involvement (specify)

21. 00. CARDIAC TUMORS

- 01. Primary tumors: Blood cysts
- 02. Focal myxomas
- 03. Intramural fibromas
- 04. Lambl's excrescences
- 05. Miscellaneous tumors
- 06. Myxomas
- 07. Pericardial tumors
- 08. Rhabdomyomas
- 09. Sarcomas
- 10. Secondary tumors

22. 00. CLOSURE OF DUCTUS IN NEWBORN PERIOD

23. 00. COARCTATION OF THE AORTA

- 03. Preductal coarctation
- 04. Preductal coarctation - operated
- 05. Postductal coarctation
- 06. Postductal coarctation - operated
- 07. Coarctation - questionable relation to ductus
- 08. Coarctation and patent ductus arteriosus
- 09. Coarctation and aortic stenosis

24. 00. CONGENITAL HEART DISEASE WITH PORTAL HYPERTENSION
(VARICES)

25. 00. CONGESTIVE HEART FAILURE

26. 00. CORONARY CALCIFICATION

27. 00. DEXTROCARDIA

- 01. With situs inversus
- 02. Without situs inversus (isolated)
- 03. Due to displacement of heart
(over)

27. 00. DEXTROCARDIA (continued)

- 04. Partial dextroversion without heart disease
- 05. Cyanotic malformation, decreased pulmonary flow with situs inversus
- 06. Cyanotic malformation, decreased pulmonary flow without situs inversus
- 07. Cyanotic malformation, increased pulmonary flow with situs inversus
- 08. Cyanotic malformation, increased pulmonary flow without situs inversus

28. 00. EBSTEIN'S DISEASE

29. 00. ECTOPIA CORDIS (DIVERTICULUM)

- 01. Ectopy of heart - abdominal
cervical
pectoral

30. 00. ELECTROCARDIOGRAMS - UNUSUAL TRACINGS (Right or left Bundle Branch Block) or simply Bundle Branch Block

31. 00. ENDOCARDIAL FIBROELASTOSIS

- 02. Primary endocardial fibroelastosis with valvular involvement (specify valve involved)
- 03. Primary endocardial fibroelastosis without valvular involvement
- 04. Secondary endocardial fibroelastosis

32. 00. FAMILIES WITH CONGENITAL HEART DISEASE

33. 00. FUNCTIONAL MITRAL INSUFFICIENCY

34. 00. FUNNEL CHEST

35. 00. GLYCOGEN STORAGE DISEASE OF THE HEART

36. 00. HYPERTENSION (SYSTEMIC) * (See "Heart Disease in Infancy & Childhood" for etiological classification)

37. 00. LEVOCARDIA

38. 00. MARFAN'S SYNDROME (ARACHNODACTYLY)

- 01. With cardiac involvement
- 02. Without cardiac involvement

39. 00. MISCELLANEOUS

- 01. Extra cardiac sound (other than venous hum)
- 02. Cardiac enlargement of any chamber - non-specific - etiology unknown

40. 00. MITRAL INSUFFICIENCY

41. 00. MITRAL ATRESIA OR MITRAL STENOSIS

- 01. Mitral atresia (aplasia)
- 02. Mitral stenosis (congenital)

42. 00. MYOCARDITIS

43. 00. NORMAL HEART (FUNCTIONAL MURMUR)

44. 00. PATENT DUCTUS ARTERIOSUS

- 01. Absence of ductus arteriosus
- 02. Aneurysm (so-called) of patent ductus arteriosus
- 03. Bilateral ductus arteriosus
- 04. Ductus - hypertensive (pulmonary pressure 70% or more of systemic)
- 05. Ductus - simple (isolated)
- 06. Patent ductus arteriosus - operated
- 07. Patent ductus arteriosus and mild coarctation
- 08. Patent ductus arteriosus, postoperative complications (Ex. aortic-bronchial fistula)
- 09. Patent ductus arteriosus and ventricular septal defect
- 10. Patent ductus arteriosus and atrial septal defect
- 11. Patent ductus arteriosus and atrial septal defect and severe pulmonary hypertension
- 12. Patent ductus arteriosus and aortic stenosis
- 13. Patent ductus arteriosus and ventricular septal defect and severe pulmonary hypertension

45. 00. PERICARDITIS

01. Absence of pericardium
02. Defect of pericardium
03. Diverticulum (or cyst) of pericardium)
04. Bacterial pericarditis (specify)
05. Constrictive pericarditis
06. Idiopathic pericarditis
07. Viral pericarditis
08. Rheumatic pericarditis
09. Rheumatoid arthritis
10. Tuberculous pericarditis
11. Uremic pericarditis
12. Post-pericardiotomy syndrome

46. 00. TRUNCUS ARTERIOSUS INCLUDING AORTIC PULMONARY
SEPTAL DEFECT (AORTIC PULMONARY WINDOW)

01. Truncus arteriosus (state group 1-4, type a, b, c, or d -
Chapter 25, "Heart Disease in Infancy & Childhood")
02. Aortic pulmonary septal defect (aortic pulmonary window)
03. Aortic pulmonary septal defect - operated

47. 00. PULMONARY ARTERIOVENOUS ANEURYSM (CONGENITAL)

48. 00. PULMONARY ARTERY ABNORMALITIES

01. Pulmonary artery dilatation
02. Bicuspid pulmonary valve
03. Absence of pulmonary valve
04. Coarctation of main pulmonary artery branch
05. Coarctation of peripheral pulmonary arteries
06. Isolated coarctation of left pulmonary artery
07. Isolated coarctation of right pulmonary artery
08. Coarctation of pulmonary artery and aorta

49. 00. METHAEMOGLOBINAEMIA

01. Congenital
02. Acquired
03. Abnormal hemoglobin other than methaemoglobinaemia

50. 00. PULMONARY ATRESIA WITH NORMAL AORTIC ROOT

51. 00. PULMONARY HEART DISEASE (COR PULMONALE)

- 01. Acute cor pulmonale (embolism)
- 02. Chronic cor pulmonale with emphysema
- 03. Chronic cor pulmonale with pulmonary hypertension
- 04. Fibrocystic disease (chronic cor pulmonale)

52. 00. PULMONARY HYPERTENSION (not included in previous diagnosis)

- 01. Primary pulmonary hypertension

53. 00. PULMONIC INSUFFICIENCY

- 01. Congenital
- 02. Acquired

54. 00. PULMONIC STENOSIS WITH NORMAL AORTIC ROOT

- 01. Combined valvular pulmonic stenosis & infundibular stenosis with normal aortic root
- 02. Infundibular stenosis with normal aortic root
- 03. Valvular pulmonic stenosis with normal aortic root (pure pulmonary stenosis)
- 04. Pulmonic stenosis with normal aortic root - operated

55. 00. RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

- 01. Acute rheumatic fever
- 02. Inactive rheumatic fever
- 03. Aortic insufficiency
- 04. Chorea
- 05. Mitral insufficiency
- 06. Mitral stenosis
- 07. Mitral valvular disease (mitral insufficiency and mitral stenosis)
- 08. Aortic stenosis (R. H. D.)
- 09. Mitral insufficiency and aortic insufficiency
- 10. Mitral insufficiency and aortic insufficiency and aortic stenosis

- 20. Complication of therapy
- 21. Cushing syndrome
- 22. Hypersalicylism

56. 00. RUBELLA DURING PREGNANCY

57. 00. SCOLIOSIS

58. 00. SINGLE VENTRICLE

01. With transposition of the great vessels
02. With pulmonary stenosis
03. Single ventricle - operated
04. With transposition of the great vessels and pulmonary stenosis
05. With tricuspid and pulmonary stenosis and/or atresia

59. 00. TETRALOGY OF FALLOT

01. Atresia of pulmonary artery branch
 02. Bicuspid pulmonary valve
 03. Combined valvular & infundibular stenosis
 04. Infundibular atresia
 05. Infundibular stenosis
 06. Pulmonary valvular atresia
 07. Valvular stenosis
 08. Pentalogy (Tetralogy of Fallot with atrial septal defect)
 09. Tetralogy of Fallot - operated - Blalock subclavian anastomosis
 10. Atypical Tetralogy of Fallot
-
20. Operated - Potts procedure - pulmonary aortic anastomosis
 21. Operated - Brock procedure - infundibulotomy
 22. Operated - Blalock - innominate to pulmonary end to side anastomosis
 23. Operated - Blalock - end to end anastomosis
 24. Operated - Blalock - other modification
-
30. Operated - open heart repair

60. 00. MONGOLISM

61. 00. TRANSPOSITION OF THE GREAT VESSELS

01. Complete transposition of the great vessels
 - 02.
 03. Transposition of the great vessels with overriding aorta
 04. Transposition of the great vessels with overriding pulmonary artery (Taussig heart)
 05. Transposition of the great vessels - operated
 06. Transposition of the great vessels - partial (both great vessels arising from one chamber)
- (over)

61. 00. TRANSPOSITION OF THE GREAT VESSELS (continued)

(Transposition with tricuspid atresia - see Tricuspid Atresia 07)

07. Transposition of the great vessels with pulmonary stenosis

62. 00. TRICUSPID ATRESIA AND STENOSIS (CONGENITAL)

01. With large ventricular septal defect

02. With pulmonary atresia

03. With pulmonary hypoplasia, with small ventricular septal defect

04. With dextrocardia

05. Tricuspid atresia - operated - Blalock anastomosis

06. Tricuspid stenosis

07. Tricuspid atresia with transposition of the great vessels

11. Operated - Potts procedure - aorta-pulmonary anastomosis

12. Operated - Glenn procedure - superior vena cava to right pulmonary artery

63. 00. TRICUSPID INSUFFICIENCY

64. 00. TWINS

65. 00. UNUSUAL THYMUS SHADOWS

66. 00. VASCULAR RINGS AND ALLIED ANOMALIES OF THE AORTIC ARCH

01. Absence of the isthmus of the aortic arch

02. Anomalous innominate artery

03. Anomalous left carotid artery

04. Anomalous subclavian from descending aorta

05. Double aortic arch (aortic ring)

06. Right aortic arch

07. Right aortic arch with left descending aorta

08. Other

09. Vascular rings and allied anomalies of the aortic arch - operated

67. 00. VENOUS HUM

68. 00. VENTRICULAR SEPTAL DEFECT

- 01. Simple (isolated)
- 02. With anomalous aortic cusp
- 03. With tricuspid insufficiency
- 04. With tricuspid valvular perforation (Ventriculo-atrial defect - shunt LV - RA)
- 05. With pulmonary hypertension (Eisenmenger's syndrome - sometimes noted as "advanced pulmonary vascular resistance")
- 06. Ventricular septal defect - operated
- 07. "Disappearing" murmur simulating ventricular septal defect
- 08. Ventricular septal defect in outflow tract of right ventricle
- 09. Ventricular septal defect and patent ductus arteriosus
- 10. Ventricular septal defect with aortic insufficiency
- 11. Ventricular septal defect with pulmonary valve stenosis
- 12. Ventricular septal defect with infundibular pulmonary stenosis with normal aortic root
- 13. Ventricular septal defect and atrial septal defect (foramen ovale or ostium secundum)

69. 00. HEMIPLEGIA

70. 00. CORRECTED TRANSPOSITION OF THE GREAT VESSELS

- 01. Corrected transposition of the great vessels - operated

71. 00. NEONATAL RESPIRATORY DISTRESS AND HYALINE MEMBRANE DISEASE (ABNORMAL PULMONARY VENTILATION, SUB-ACUTE COR PULMONALE)

72. 00. ASPLENIA, OR ABSENCE OF THE SPLEEN

APPENDIX C

PEDIATRIC CARDIAC RESEARCH PROJECT
OF THE
NEW HAVEN RHEUMATIC FEVER AND CARDIAC PROGRAM
IN COOPERATION WITH THE
CONNECTICUT STATE DEPARTMENT OF HEALTH
AND
DEPARTMENT OF PEDIATRICS. YALE UNIVERSITY SCHOOL OF MEDICINE
YALE-NEW HAVEN MEDICAL CENTER

RUTH WHITTEMORE, M.D., DIRECTOR

ADDRESS:
333 CEDAR STREET
NEW HAVEN 11, CONN.
TELEPHONE LOCUST 2-1161 EXT. 798 or 731

Dear

Re:

You may remember that your child was seen by the doctors in the New Haven Rheumatic Fever and Cardiac Clinic several years ago because of a suspected heart condition. Of the children examined by us, some were found to have only an innocent or functional murmur; others had congenital, rheumatic or some other form of heart disease.

Information gathered on the 5,000 patients we saw may be helping us to understand certain factors concerning heart disease in children. This letter is to request you to help us better answer some important research questions. We are now anxious to obtain more family information in a proportion of our former patients with a heart condition as well as those with only an innocent murmur. Enclosed is a questionnaire asking for certain specific information to complete our records concerning the family history. As we wish to know about all of your children, please fill out the entire form, even if this repeats some (or all) of the information already given. This will be held in the strictest confidence. Physicians will be contacted only if necessary to give pertinent facts concerning any heart problem.

If there are any questions about this study or, in fact, concerning the patient who was seen in our clinic, please do not hesitate to communicate with me. In many cases, we have not seen you for many years; some are still coming to clinic, others have undoubtedly moved or the patient may now have grown up. In a few instances, this letter will come to parents who have unfortunately lost their child. In all cases, however, we are most desirous of your help. We are also anxious to hear how the patient and his family is doing. Do tell us in the space provided for comments. Thank you for your assistance in compiling this important information.

Sincerely, and with grateful appreciation,

Ruth Whittemore, M. D.

RW/cfm
Enclosure

Name of Patient _____ BD _____

Name Date of Birth Place of Birth State of Health*

I Mother
(Maiden Name) _____
Father _____
Indicate if adoptive _____ or foster _____ parents.
Have you (mother) ever been told you had a heart condition? _____
Has the father? _____
If so, what is the nature of the condition? _____
What doctor would know about this condition? _____

II Brothers and sisters of the patient -- (living or deceased) --
Please list all -- preferably in order -- and indicate abnormalities or health problems. Have any had a heart condition?
(If step-children, please specify whether of father or mother)

<u>Name</u>	<u>Birth Date</u>	<u>Birth Place</u>	<u>State of Health*</u>
Ex.: Mary Jones	6/10/49	Watertown, Conn.	Died 9/20/49 Waterbury Hospital, cleft palate and "blue baby" -- Dr. Allen Smith (autopsy performed)

(Use next page if necessary)

What doctor knows most about your children? _____

May we have permission to contact either physician if necessary? Yes ___ No ___

III Did you (mother) ever lose any pregnancy either before or since the birth of the patient (miscarriages, abortions, or stillbirths)? _____ If so, please give approximate dates and age of the pregnancy when lost:

<u>Date</u>	<u>Age of Pregnancy</u>

* If deceased -- please give date, place (name of hospital if known) and cause of death and name of doctor, if known.

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IV If mother and father of patient have separated or been divorced, have there been subsequent pregnancies in either case?_____ If so, please list and designate. (If included under Question II please indicate)_____

Please give the address of the former spouse if known:

V In some instances, the patient named at the top may have been married and become a parent. If so, please:

1. Give current name and address of patient:_____

2. Number of Children:_____

Additional Space for Answers (designate number of question)

Comments

Please sign Name_____

Current Address_____

Relationship (if
other than mother)

Return to: Ruth Whittemore, M. D.
333 Cedar Street
New Haven, Connecticut

Thank You.

(stamped envelope enclosed)

